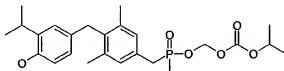


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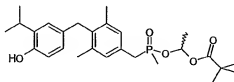
mm; Mobile phase = Solvent A: H<sub>2</sub>O/0.05% TFA; Solvent B: ACN/0.05% TFA. Flow rate = 2.0 mL/min; UV@ 254 nm. Retention time in minutes. (rt = 10.05/20.00, 93% purity). TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = 100% EtOAc; R<sub>f</sub> = 0.28.

**Compound 12-15:** Isopropoxyxycarbonyloxymethyl [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-methylphosphinate



[0646] The title compound was prepared from [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-methylphosphinic acid (example 72) according to the procedure described for the synthesis of Example 12, compound 12-3. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.02 (d, *J* = 2.4 Hz, 2H), 6.8 (s, 1H), 6.57-6.62 (m, 2H), 5.61-5.66 (m, 2H), 4.90-4.93 (m, 1H), 3.96 (s, 2H), 3.20 (m, 1H), 2.25 (s, 6H), 1.50 (d, *J* = 14.1 Hz, 3H), 1.20 (m, 6H), 1.13 (m, 6H); LC-MS *m/z* = 463 [C<sub>25</sub>H<sub>35</sub>O<sub>6</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>25</sub>H<sub>35</sub>O<sub>6</sub>P+0.3 H<sub>2</sub>O): C, 64.17; H, 7.62. Found: C, 64.01; H, 7.62; HPLC conditions: Column = Waters Atlantis; dC18-150×4.6 mm; Mobile phase = Solvent A: H<sub>2</sub>O/0.05% TFA; Solvent B: ACN/0.05% TFA. Flow rate = 2.0 mL/min; UV@ 254 nm. Retention time in minutes. (rt = 9.60/20.00, 92% purity). TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = 100% EtOAc; R<sub>f</sub> = 0.28.

**Compound 12-16:** 1-(Pivaloyloxyethyl)[3,5-dimethyl-4-(4'-hydroxy-3'-iso-propylbenzyl)benzyl]methylphosphinate



Step a:

[0647] To a mixture of acetaldehyde (0.84 mL, 16.6 mmol) in zinc chloride (62 mg, 0.45 mmol) was added dropwise 2,2-dimethyl-propionaldehyde (2.05

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mL, 16.6 mmol). The mixture was then heated to 50 °C for 16 h. The blackish material was filtered through a plug of silica gel with dichloromethane to afford 2,2-dimethyl-propionic acid 1-chloro-ethyl ester as an oil (2.4 g, 88 %) after the removal of dichloromethane under reduced pressure:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.64-6.59 (m, 1H), 1.82 (d,  $J = 6.7$  Hz, 3H), 1.36 (s, 9H).

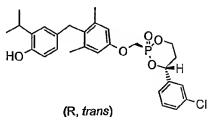
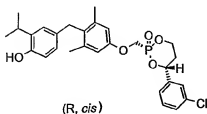
Step b:

[0648] To a mixture of 2,2-dimethyl-propionic acid 1-chloro-ethyl ester (2.4 g, 14.6 mmol) in acetonitrile (10 mL) was added sodium iodide (4.4 g, 30.0 mmol). The mixture was stirred in the absence of light for 16 h. The volatiles were removed under reduced mixture, taken up in hexanes (25 mL) and filtered through a plug of silica gel to afford 2,2-dimethyl-propionic acid 1-iodo-ethyl ester as oil (1 g, 27 %) after the removal of hexanes under reduced pressure:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.92-6.85 (m, 1H), 2.21 (d, 3H), 1.36 (s, 9H).

Step c:

[0649] The title compound was prepared from 3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)benzyl)methylphosphinic acid (example 72) according to the procedure described for the synthesis of Example 12, compound 12-1.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.30-6.94 (m, 3H), 6.64-6.60 (m, 1H), 6.53-6.50 (m, 1H), 3.95 (s, 2H), 3.39-3.08 (m, 3H), 2.21 (s, 6H), 1.64-1.20 (m, 21H), 1.13 (t, 6H); LC-MS  $m/z = 475.6$  [ $\text{C}_{27}\text{H}_{39}\text{O}_5\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{27}\text{H}_{39}\text{O}_5\text{P} + 0.4 \text{H}_2\text{O}$ ): C, 68.33; H, 8.28. Found: C, 68.09; H, 8.29.

**Example 12-16:** *Cis* and *Trans* *R*-2-[(3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy)methyl]-4-(3-chlorophenyl)-2-oxo-2 $\lambda^5$ -[1,3,2]-dioxaphosphonane



[0650] The title compounds were prepared from *R*-1-(3-chlorophenyl)-1,3-propanediol and [3,5-dimethyl-4-(3'-*iso*-propyl-4'-hydroxybenzyl)phenoxy]-methylphosphonic acid (compound 7) according to the procedure described in example 13-1.

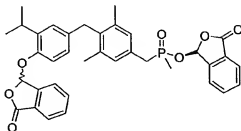
**Example 12-16-*cis*:**

MP 72-75 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.00 (s, 1H), 7.51 (m, 1H), 7.38-7.36 (m, 3H), 6.86 (d, *J* = 2.0 Hz, 1H), 6.77 (s, 2H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.43 (m, 1H), 5.76-5.71 (m, 1H), 4.61-4.36 (m, 4H), 3.83 (s, 2H), 3.15-3.05 (m, 1H), 2.24-2.17 (m, 2H), 2.14 (s, 6H), 1.12 (d, *J* = 6.9 Hz, 6H); LC-MS *m/z* = 515 [C<sub>28</sub>H<sub>32</sub>ClO<sub>5</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>28</sub>H<sub>32</sub>ClO<sub>5</sub>P + 0.2 H<sub>2</sub>O + 0.2 CH<sub>3</sub>COCH<sub>3</sub>): C, 64.79; H, 6.39; Cl, 6.69. Found: C, 64.86; H, 6.48; Cl, 6.70; TLC conditions: Uniplat silica gel, 250 microns; mobile phase = 4:1 ethyl acetate-hexanes; R<sub>f</sub> = 0.19.

**Example 12-16-*trans*:**

MP 81-83 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.00 (s, 1H), 7.50 (m, 1H), 7.49-7.43 (m, 3H), 6.87 (d, *J* = 2.0 Hz, 1H), 6.84 (s, 2H), 6.63 (d, *J* = 11.0 Hz, 1H), 6.47 (m, 1H), 5.82 (m, 1H), 4.80 (m, 1H), 4.65 (d, *J* = 16.0 Hz, 2H), 3.83 (s, 2H), 3.14 (m, 1H), 2.24-2.17 (m, 8H), 1.13 (d, *J* = 6.9 Hz, 6H); LC-MS *m/z* = 515 [C<sub>28</sub>H<sub>32</sub>ClO<sub>5</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>28</sub>H<sub>32</sub>ClO<sub>5</sub>P + 0.2 H<sub>2</sub>O + 0.2 CH<sub>3</sub>COCH<sub>3</sub>): C, 64.79; H, 6.39; Cl, 6.69. Found: C, 65.02; H, 6.46; Cl, 6.54; TLC conditions: Uniplat silica gel, 250 microns; mobile phase = 4:1 ethyl acetate-hexanes; R<sub>f</sub> = 0.44.

**Compound 12-17:** (3-Oxo-1,3-dihydro-isobenzofuran-1-yl){3,5-dimethyl-4-[3'-isopropyl-4'-(3-oxo-1,3-dihydro-isobenzofuran-1-yloxy)benzyl]benzyl}-methyl-phosphinate



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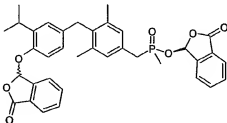
Step a:

[0651] To a mixture of 3H-isobenzofuran-1-one (1.34 g, 10.0 mmol) in carbon tetrachloride (10 mL) was added NBS (2.0 g, 11.0 mmol), and AIBN (0.16 g, 1.0 mmol). The mixture was then heated to reflux for 2 h. Water and dichloromethane were added and the layers were separated. The organic layer was then dried over sodium sulfate, filtered and removed under reduced pressure. The mixture was subjected to medium pressure column chromatography (ISCO), eluting with hexanes to 100% ethyl acetate-hexanes to afford 3-bromo-3H-isobenzofuran-1-one as a white solid (1.8 g, 85 %). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.97 (d, *J* = 8.1 Hz, 1H), 7.83–7.80 (t, *J* = 7.5 Hz, 1H), 7.69–7.64 (m, 2H), 7.44 (s, H).

Step b:

[0652] The title compound was prepared from 3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)benzyl]methylphosphinic acid (example 72) according to the procedure described for the synthesis of Example 12, compound 12-1. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.05-7.60 (m, 7H), 7.85-6.84 (m, 5H), 4.06 (d, *J* = 14.1 Hz, 2H), 3.30-3.07 (m, 3H), 2.28 (d, *J* = 8.7 Hz, 6H), 1.74 (d, *J* = 12.0 Hz, 3H), 1.23-1.15 (m, 6H); LC-MS *m/z* = 611.6 [C<sub>36</sub>H<sub>35</sub>O<sub>7</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>36</sub>H<sub>35</sub>O<sub>7</sub>P + 1.7 H<sub>2</sub>O): C, 67.43; H, 6.04. Found: C, 67.12; H, 6.22.

**Compound 12-18:** (3-oxo-1,3-dihydro-isobenzofuran-1-yl){3,5-Dimethyl-4-[3'-isopropyl-4'-(3-oxo-1,3-dihydro-isobenzofuran-1-yloxy)benzyl]benzyl}-methyl-phosphinate

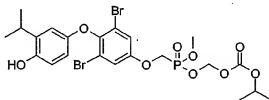




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[0653] The title compound was prepared from 3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)benzyl]methylphosphinic acid (example 72) according to the procedure described for the synthesis of Example 12, compound 12-1.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.05-7.30 (m, 8H), 7.26-7.07 (m, 1H), 7.03-6.96 (m, 3H), 6.80-6.74 (m, 1H), 4.05 (d,  $J = 14.1$  Hz, 2H), 3.49-3.27 (m, 2H), 3.08-3.02 (m, 1H), 2.28 (d,  $J = 9.3$  Hz, 6H), 1.53 (dd,  $J = 10.8, 14.1$  Hz, 3H), 1.32-1.12 (m, 6H); LC-MS  $m/z = 611.6$  [ $\text{C}_{36}\text{H}_{35}\text{O}_7\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{36}\text{H}_{35}\text{O}_7\text{P}$ ): C, 70.81; H, 5.78. Found: C, 71.08; H, 6.19.

**Example 12-19:** Isopropylloxycarbonyloxymethyl[3,5-dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)]phenoxy]methylphosphonate monomethyl ester



[0654] The title compound was prepared from [3,5-dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)]phenoxy]methylphosphonate monomethyl ester (compound 69-6) according to the procedures described for the synthesis of compound 12-3.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.04 (s, 1H), 7.50 (s, 2H), 6.66 (m, 2H), 6.28 (m, 1H), 5.69 (d,  $J = 12.0$  Hz, 2H), 4.84 (m, 1H), 4.66 (d,  $J = 15.0$  Hz, 2H), 3.80 (d,  $J = 20.0$  Hz, 3H), 3.17 (m, 1H), 1.24 (m, 7H), 1.14 (m, 7H); LC-MS  $m/z = 627$  [ $\text{C}_{22}\text{H}_{27}\text{Br}_2\text{O}_9\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{22}\text{H}_{27}\text{Br}_2\text{O}_9\text{P} + 0.3 \text{ CH}_3\text{COCH}_3$ ): C, 42.73; H, 4.51. Found: C, 43.09; H, 4.18; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate;  $R_f = 0.64$ .

### Example 13

*Cis* and *Trans* (*S*)-2-[(3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy)methyl]-4-(3-chlorophenyl)-2-oxo-2 $\lambda^2$ -[1,3,2]-dioxaphosphonane

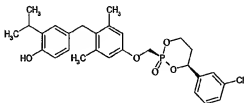
[0655] To a mixture of [4-(4'-hydroxy-3'-*iso*-propylbenzyl)-3,5-dimethylphenoxy] methylphosphonic acid (0.2 g, 0.55 mmol), 1-(3-chlorophenyl)-1,3-propane diol (0.31 g, 1.6 mmol) and pyridine (1 mL)

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in DMF (5 mL) at room temperature was added 1,3-dicyclohexylcarbodiimide (0.34 g, 1.6 mmol). The reaction mixture was heated at 70 °C for 4 h, cooled to room temperature and filtered through a Celite plug. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel, eluting with 4% methanol in CH<sub>2</sub>Cl<sub>2</sub> to afford *Cis* (0.06 g, 15%) and *Trans* (*S*)-2-[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl) phenoxy]methyl-4-(3-chlorophenyl)-2-oxo-1,3,2-dioxaphosphonane (0.05 g, 12%) as white solids.

**Compound 13-1-*cis*:**

[0656] mp 77-82 °C; LC-MS *m/z* = 516 [C<sub>28</sub>H<sub>32</sub>ClO<sub>5</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>28</sub>H<sub>32</sub>ClO<sub>5</sub>P+0.2 H<sub>2</sub>O): C, 64.85; H, 6.30. Found: C, 64.93; H, 6.65. M.P.: 77-82.0 °C.



[0657] Alternative improved method for the preparation of compound:

**Compound 13-1-*cis*:** *Cis* (*S*)-2-[(4-(4'-acetoxo-3'-*iso*-propylbenzyl)phenoxy)methyl]-4-(3-Chlorophenyl)-2-oxo-2λ<sup>5</sup>-[1,3,2]-dioxaphosphinane:

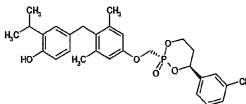
[0658] A solution of *cis* (*S*)-2-[(4-(4'-acetoxo-3'-*iso*-propylbenzyl)-3,5-dimethylphenoxy)methyl]-4-(3-chlorophenyl)-2-oxo-2λ<sup>5</sup>-[1,3,2]-dioxaphosphonane (compound 59-*cis*, 2.5 g, 4.49 mmol) and 4.0 M HCl in dioxane (2.5 mL, 10.0 mmol) in methanol (25 mL) was stirred at 20 °C for 3.5 hrs. The solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with acetone-dichloromethane (1:4) to afford *cis* (*S*)-2-[(3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy)methyl]-4-(3-Chlorophenyl)-2-oxo-2λ<sup>5</sup>-[1,3,2]-dioxaphosphinane (1.9g, 83%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.97 (s, 1H), 7.47 (m, 1H), 7.38-7.31 (m, 3H), 6.82 (d, *J* = 2.1 Hz, 1H), 6.73 (s, 2H), 6.59 (d, *J* = 8.1 Hz, 1H), 6.43 (dd, *J* = 8.1 and 2.0 Hz, 1H), 5.76-5.71 (m, 1H),

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4.61-4.36 (m, 4H), 3.78 (s, 2H), 3.15-3.05 (m, 1H), 2.24-2.17 (m, 2H), 2.14 (s, 6H), 1.07 (d,  $J = 6.9$  Hz, 6H). TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = dichloromethane-acetone (9:1);  $R_f = 0.28$ ; Anal Calcd for  $(C_{28}H_{32}ClO_5P + 0.2 H_2O)$ : C, 64.85; H, 6.30. Found: C, 64.64; H, 6.36. Water by KF titration = 0.66%.

**Compound 13-1-trans:**

[0659] mp 88-93 °C; LC-MS  $m/z = 516$   $[C_{28}H_{32}ClO_5P + H]^+$ ; Anal. Calcd for  $(C_{28}H_{32}ClO_5P + 0.2 H_2O)$ : C, 64.85; H, 6.30. Found: C, 64.93; H, 6.65. M.P.: 88-93.0 °C.

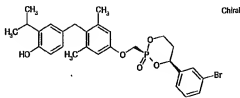


[0660] Using the appropriate starting material, compounds 13-2 to 13-14 were prepared in an analogous manner to that described for the synthesis of compound 13-1.

[0661] *Cis* and *Trans* 2-[(3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy)methyl]-4-(3-bromophenyl)-2-oxo-2λ<sup>5</sup>-[1,3,2]-dioxaphosphonane:

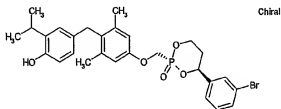
**Compound 13-2-cis:**

[0662] mp 70-75 °C; LC-MS  $m/z = 559, 561$   $[C_{28}H_{32}BrO_5P + H]^+$ ; Anal. Calcd for  $(C_{28}H_{32}BrO_5P)$ : C, 60.12; H, 5.77. Found: C, 60.03, H, 5.76; TLC conditions: Uniplate silica gel, 250 microns; mobile phase = 3:2 hexanes-acetone;  $rf = 0.31$ .

**Compound 13-2-trans:**

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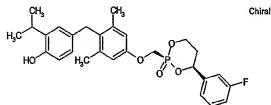
- [0663] mp 80-85 °C; LC-MS  $m/z$  = 559,561 [ $C_{28}H_{32}BrO_3P + H$ ]<sup>+</sup>; Anal. Calcd for ( $C_{28}H_{32}BrO_3P$ ): C, 60.12; H, 5.77. Found: C, 59.76, H, 5.72; TLC conditions: Uniplat silica gel, 250 microns; mobile phase = 3:2 hexanes-acetone;  $r_f$  = 0.49.



- [0664] *Cis* and *Trans* 2-[(3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)phenoxy)methyl]-4-(3-fluorophenyl)-2-oxo-2,3-dihydro-1,3,2-dioxaphosphonane:

**Compound 13-3-*cis*:**

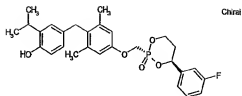
- [0665] mp 75-80 °C; LC-MS  $m/z$  = 499 [ $C_{28}H_{32}FO_3P + H$ ]<sup>+</sup>; Anal. Calcd for ( $C_{28}H_{32}FO_3P + 0.2$  EtOAc): C, 67.02; H, 6.56. Found: C, 67.01, H, 6.58; TLC conditions: Uniplat silica gel, 250 microns; mobile phase = 3:2 acetone-hexanes;  $r_f$  = 0.19.



**Compound 13-3-*trans*:**

- [0666] mp 80-85 °C; LC-MS  $m/z$  = 499 [ $C_{28}H_{32}FO_3P + H$ ]<sup>+</sup>; Anal. Calcd for ( $C_{28}H_{32}FO_3P + 0.2$  EtOAc): C, 67.02; H, 6.56. Found: C, 66.93, H, 6.61; TLC conditions: Uniplat silica gel, 250 microns; mobile phase = 3:2 acetone-hexanes;  $r_f$  = 0.52.

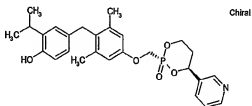
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[0667] *Cis* and *Trans* 2-[(3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy) methyl]-4-(pyrid-3-yl)-2-oxo-2λ<sup>5</sup>-[1,3,2]-dioxaphosphonane:

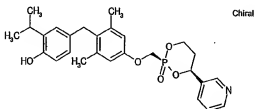
**Compound 13-4-*trans*:**

[0668] mp 75-78 °C: LC-MS  $m/z$  = 482 [C<sub>27</sub>H<sub>32</sub>NO<sub>5</sub>P+H]<sup>+</sup>; Anal Calcd for C<sub>27</sub>H<sub>32</sub>NO<sub>5</sub>P: C, 67.35; H, 6.70; N, 2.91. Found: C, 67.17; H, 6.89; N, 2.62; TLC conditions: Uniplat silica gel, 250 microns; mobile phase = CH<sub>2</sub>Cl<sub>2</sub>-MeOH (2%); R<sub>f</sub> = 0.3.



**Compound 13-4-*cis*:**

[0669] (108 mg, 50%): mp 75-78 °C; LC-MS  $m/z$  = 482 [C<sub>27</sub>H<sub>32</sub>NO<sub>5</sub>P+H]<sup>+</sup>; Anal Calcd for C<sub>27</sub>H<sub>32</sub>NO<sub>5</sub>P: C, 67.35; H, 6.70; N, 2.91. Found: C, 67.78; H, 6.76; N, 2.63; TLC conditions: Uniplat silica gel, 250 microns; mobile phase = CH<sub>2</sub>Cl<sub>2</sub>-MeOH (2%); R<sub>f</sub> = 0.27.

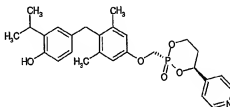


[0670] *Cis* and *Trans* 2-[(3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy)methyl]-4-(pyrid-4-yl)-2-oxo-2λ<sup>5</sup>-[1,3,2]-dioxaphosphonane:

**Compound 13-5-*trans*:**

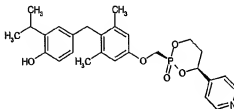
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- [0671] (52%), mp 75-77 °C; LC-MS  $m/z$  = 482  $[C_{27}H_{32}NO_5P+H]^+$ ; Anal Calcd for  $(C_{27}H_{32}NO_5P+0.4 H_2O)$ : C, 66.35; H, 6.76; N, 2.87. Found: C, 66.08; H, 6.55; N, 2.74; TLC conditions: Uniplat silica gel, 250 microns; mobile phase =  $CH_2Cl_2$ -MeOH (2%);  $R_f$  = 0.3.



**Compound 13-5-cis:**

- [0672] (20%), mp 75-77 °C; LC-MS  $m/z$  = 482  $[C_{27}H_{32}NO_5P+H]^+$ ; Anal Calcd: (MF:  $C_{27}H_{32}NO_5P$ ) Calcd: C:67.35, H:6.70, N:2.91; Found: C: 67.02, H:6.78, N:2.81; TLC conditions: Uniplat silica gel, 250 microns; mobile phase =  $CH_2Cl_2$ -MeOH (2%);  $R_f$  = 0.25.

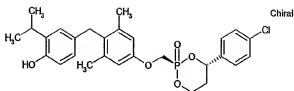


- [0673] *Cis* and *Trans* 2-[(3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy)methyl]-4-(4-chlorophenyl)-2-oxo-2λ<sup>5</sup>-[1,3,2]-dioxaphosphonane:

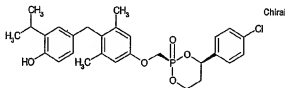
**Compound 13-6-trans:**

- [0674] mp 77-80 °C; LC-MS  $m/z$  = 515  $[C_{28}H_{32}ClO_5P]^+$ ; Anal Calcd: (MF:  $C_{28}H_{32}ClO_5P+0.1 H_2O+0.4 EtOAc$ ) Calcd: C:64.34, H:6.48; Found: C: 64.56, H:6.91; TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate/hexanes (3:2);  $R_f$  = 0.6.

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**Compound 13-6-cis:**

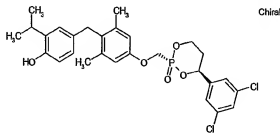
- [0675] yellow solid, mp 77-80 °C; LC-MS  $m/z$  = 515  $[C_{28}H_{32}ClO_5P+H]^+$ ; Anal Calcd: (MF:  $C_{28}H_{32}ClO_5P+0.1 H_2O+0.1 CH_2Cl_2$ ) Calcd: C:64.65, H:6.25; Found: C:64.61, H:6.66; TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate/hexanes (3:2);  $R_f$  = 0.5.



- [0676] *Cis* and *Trans* 2-[(3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy)methyl]-4-(3,5-dichlorophenyl)-2-oxo-2λ<sup>5</sup>-[1,3,2]-dioxaphosphonane:

**Compound 13-7-trans:**

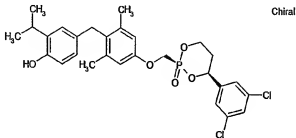
- [0677] mp 79-81 °C; LC-MS  $m/z$  = 549  $[C_{27}H_{32}Cl_2O_5P+H]^+$ ; Anal Calcd for ( $C_{28}H_{31}Cl_2O_5P+0.35 H_2O$ ): C, 60.45; H, 5.74; Cl, 12.87. Found: C, 60.15; H, 5.67, Cl, 11.97; TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate/hexanes (3:2);  $R_f$  = 0.6.

**Compound 13-7-cis:**

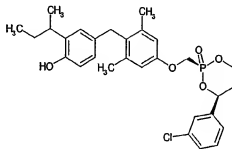
- [0678] (50%) mp 79 - 81 °C; LC-MS  $m/z$  = 549  $[C_{28}H_{31}Cl_2O_5P]^+$ ; Anal Calcd for ( $C_{28}H_{31}Cl_2O_5P+0.1 H_2O$ ): C, 60.94; H, 5.70; Cl, 12.97. Found: C, 60.77;

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H, 6.18; Cl, 11.56; TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (3:2);  $R_f$  = 0.5.



**Compound 13-8:** *Cis-(S)*-2-[(3,5-dimethyl-4-(4'-hydroxy-3'-sec-butylbenzyl)phenoxy)methyl]-4-(3-chlorophenyl)-2-oxo-2λ<sup>5</sup>-[1,3,2]-dioxaphosphonane

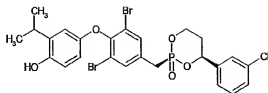


[0679] mp: 66-70 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.91 (s, 1 H), 7.39-7.36 (m, 3H), 6.76 (s, 1H), 6.75 (s, 2H), 6.60-5.57 (d, 1H), 6.47-6.44 (d, 1H), 5.75-5.71 (m, 1H), 4.61-4.53 (m, 2H), 4.47-4.36 (m, 2H), 3.78 (s, 2H), 2.92-2.85 (q, 1H), 2.25-2.20 (m, 2H), 2.14 (s, 6H), 1.51-1.36 (m, 2H), 1.05-1.03 (d, 3H), 0.74-0.70 (t, 3H); LC-MS *m/z* = 529.0 [C<sub>29</sub>H<sub>34</sub>ClO<sub>5</sub>P + H]<sup>+</sup>; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (1:1);  $R_f$  = 0.17; Anal. Calcd for (C<sub>29</sub>H<sub>34</sub>ClO<sub>5</sub>P + 0.3 CH<sub>3</sub>CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> + 0.4 H<sub>2</sub>O): C, 64.47; H, 6.66. Found: C, 64.64; H, 6.82.

**Compound 13-9:** *Cis-(S)*-2-[3,5-dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)benzyl]-4-(3-chlorophenyl)-2-oxo-2λ<sup>5</sup>-[1,3,2]-dioxaphosphonane

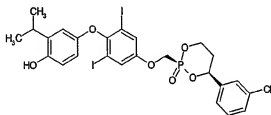


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[0680] mp: 83-85 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.06 (s, 1H), 7.75 (s, 2H), 7.44-7.42 (m, 3H), 7.32-7.28 (m, 1H), 6.68-6.65 (d, 1H), 6.58 (s, 1H), 6.31-6.27 (d, 1H), 5.69-5.65 (d, 1H), 4.59-4.51 (t, 1H), 4.37-4.28 (t, 1H), 3.61-3.53 (d, 2H), 3.18-3.07 (m, 1H), 2.29-2.17 (m, 1H), 1.84-1.77 (m, 1H), 1.07-1.03 (d, 6H); LC-MS  $m/z$  = 630.8  $[\text{C}_{25}\text{H}_{24}\text{Br}_2\text{ClO}_5\text{P} + \text{H}]^+$ ; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (1:1);  $R_f$  = 0.56; Anal. Calcd for  $(\text{C}_{25}\text{H}_{24}\text{Br}_2\text{ClO}_5\text{P})$ : C, 47.61; H, 3.84. Found: C, 47.88; H, 4.23.

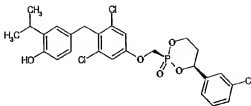
**Compound 13-10:** *Cis* (S)-2-[(3,5-diiodo-4-(4'-hydroxy-3'-isopropylphenoxy)methyl)-4-(3-chlorophenyl)-2-oxo-2 $\lambda^5$ -[1,3,2]-dioxaphosphonane



[0681] mp: 82-86 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.99 (s, 1H), 7.62 (s, 1H), 7.51 (m, 1H), 7.44 (s, 2H), 7.38 (m, 3H), 6.68 (m, 1H), 6.60 (s, 1H), 6.25 (m, 1H), 5.80 (m, 1H), 4.65 (m, 3H), 4.45 (m, 1H), 3.16 (m, 1H), 2.26 (m, 1H), 1.13 (d,  $J$  = 6.0 Hz, 6H); LC-MS  $m/z$  = 741  $[\text{C}_{25}\text{H}_{24}\text{ClI}_2\text{O}_6\text{P} + \text{H}]^+$ ; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (4:1);  $R_f$  = 0.17. Anal. Calcd for  $(\text{C}_{25}\text{H}_{24}\text{ClI}_2\text{O}_6\text{P} + 0.2 \text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3)$ : C, 40.86; H, 3.40. Found: C, 41.02, H, 3.49.

**Compound 13-11:** *Cis* (S)-2-[(3,5-dichloro-4-(4'-hydroxy-3'-isopropylbenzyl)phenoxy)methyl]-4-(3-chlorophenyl)-2-oxo-2 $\lambda^5$ -[1,3,2]-dioxaphosphonane

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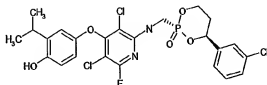


[0682]  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  9.10 (s, 1 H), 7.43 (s, 1 H), 7.38-7.31 (m, 4 H), 7.24 (m, 1 H), 6.97 (s, 1 H), 6.64 (s, 2 H), 5.75 (m, 1 H), 4.69-4.61 (m, 2 H), 4.50-4.41 (m, 2 H), 4.05 (s, 2 H), 3.12 (m, 1 H), 2.21 (s, 2 H), 1.11 (d,  $J$  = 9.0 Hz, 6 H); LC-MS  $m/z$  = 554 [ $\text{C}_{26}\text{H}_{26}\text{Cl}_3\text{O}_3\text{P} + \text{H}$ ] $^+$ ; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (4:1);  $R_f$  = 0.24. Anal. Calcd for ( $\text{C}_{26}\text{H}_{26}\text{Cl}_3\text{O}_3\text{P} + 0.5 \text{H}_2\text{O} + 0.2 \text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$ ): C, 55.27; H, 4.95. Found: C, 55.21, H, 4.96.

*Cis* and *Trans* 2-[4,6-dichloro-3-fluoro-5-(4'-hydroxy-3'-*iso*-propylphenoxy)-pyrid-2-ylaminomethyl]-4-(3-chlorophenyl)-2-oxo-2 $\lambda^5$ -[1,3,2]-dioxaphosphonane

[0683] To a stirring solution of [4,6-dichloro-3-fluoro-5-(4'-hydroxy-3'-*iso*-propylphenoxy)-pyrid-2-ylamino]methylphosphonic (0.2 g, 0.47 mmol, US 6747048 B2) and (S)-1-(3-chlorophenyl)-1,3-propanediol (0.18 g, 0.94 mmol) in DMF (6 mL) at room temperature was added pyridine (0.46 mL, 5.64 mmol) and EDCI (0.27 g, 1.41 mmol). The reaction mixture was stirred at 68 °C for 16 hrs. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and water. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate to afford:

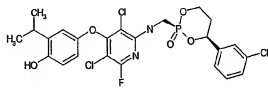
**Compound 13-12-*trans*:**



[0684] (60 mg, 22%):  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  9.20 (s, 1 H), 7.67 (t,  $J$  = 6.0 Hz, 1 H), 7.36-7.48 (m, 4 H), 6.81 (d,  $J$  = 3.0 Hz, 1 H), 6.69 (d,  $J$  = 9.0

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Hz, 1 H), 6.44 (dd,  $J = 3.0, 9.0$  Hz, 1 H), 5.78 (t,  $J = 7.5$  Hz, 1 H), 4.71 (m, 1 H), 4.45 (m, 1 H), 4.11 (m, 2 H), 3.17 (m, 1 H), 2.19 (s, 1 H), 1.14 (d,  $J = 6.9$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (2:1);  $R_f = 0.44$ ; LC-MS  $m/z = 576$  [ $C_{24}H_{23}Cl_3FN_2O_5P + H$ ] $^+$ ; Anal Calcd for ( $C_{24}H_{23}Cl_3FN_2O_5P + 0.2CH_2Cl_2 + 0.3H_2O$ ): C, 48.58; H, 4.04; N, 4.68. Found: C, 48.64; H, 3.66; N, 4.83.

**Compound 13-12-cis:**

[0685] (90 mg, 33%):  $^1H$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  9.20 (s, 1 H), 7.67 (t,  $J = 6.0$  Hz, 1 H), 7.21-7.37 (m, 4 H), 6.71 (d,  $J = 3.0$  Hz, 1 H), 6.63 (d,  $J = 9.0$  Hz, 1 H), 6.34 (dd,  $J = 3.0, 9.0$  Hz, 1 H), 5.65 (d,  $J = 10.4$  Hz, 1 H), 4.21 – 4.61 (m, 2 H), 4.11 (m, 1 H), 3.80 (m, 1 H), 3.07 (m, 1 H), 2.11 (m, 1 H), 1.88 (m, 1 H), 1.04 (m, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate;  $R_f = 0.53$ ; LC-MS  $m/z = 576$  [ $C_{24}H_{23}Cl_3FN_2O_5P + H$ ] $^+$ ; Anal Calcd for ( $C_{24}H_{23}Cl_3FN_2O_5P + 0.1CH_2Cl_2 + 0.4H_2O$ ): C, 48.94; H, 4.09; N, 4.74. Found: C, 48.57; H, 3.69; N, 4.92.

Step a:

[0686] To a solution of diisopropyl amine (12.4 mL, 88.2 mmol) in THF (50 mL) at  $-78$  °C was added n-butyllithium (35.3 mL, 88.2 mmol). The reaction mixture was stirred at  $-78$  °C for 30 min, at which time ethyl acetate was added (16.1 mL, 163.2 mmol). After 1 h, 3-chlorobenzaldehyde was added and the reaction mixture was allowed to warm to room temperature over 2h. The reaction mixture was quenched with aqueous saturated  $NH_4Cl$  (20 mL) and extracted with ethyl acetate (2 x 20mL). The organic layer was rinsed with water (20 mL) and brine (20 mL), dried over  $Na_2SO_4$ , filtered and concentrated under reduced pressure to afford yellow oil. The crude product was purified by column chromatography on silica gel, eluted with ethyl

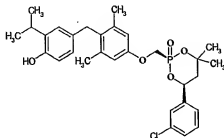
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acetate-hexanes (1:4) to afford ethyl 3-(3-chloro-phenyl)-3-hydroxy-propionate as a yellow oil (10.0 g, 99.0 %).  $^1\text{H}$  NMR (400 MHz, d-DMSO):  $\delta$  7.43-7.30 (m, 4H), 5.66 (d, 1H), 5.01-4.95 (q, 1H), 4.14-4.04 (m, 2H), 2.71-2.58 (m, 2H), 1.24-1.17 (t, 3H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:3);  $R_f$  = 0.50.

Step b:

[0687] To a solution of ethyl 3-(3-chloro-phenyl)-3-hydroxy-propionate (10.0g, 44.1 mmol) in THF (100 mL) and diethyl ether (100 mL) at  $-78^\circ\text{C}$  was added methyl magnesium bromide (61.7 mL of a 3.0M solution in diethyl ether, 185.1 mmol). The reaction mixture was allowed to warm to room temperature and stir for 16 h. The reaction mixture was cooled to  $-50^\circ\text{C}$  and quenched with aqueous saturated  $\text{NH}_4\text{Cl}$  (20mL), and extracted with diethyl ether (2 x 20 mL). The organic layer was rinsed with water (20 mL) and brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluted with ethyl acetate-hexanes (1:3) to afford 1-(3-Chloro-phenyl)-3-methyl-butane-1,3-diol as a yellow oil (5.65 g, 59.7 %).  $^1\text{H}$  NMR (400 MHz, d-DMSO):  $\delta$  7.40-7.26 (m, 4H), 5.46 (d, 1H), 4.90-4.85 (q, 1H), 4.70 (s, 1H), 1.75-1.62 (m, 2H), 1.23-1.22 (d, 3H), 1.19-1.18 (d, 3H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:3);  $R_f$  = 0.32.

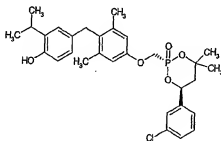
**Compound 13-13-cis:** *Cis* 2-[(3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy)methyl]-4,4-dimethyl-6-(3-chlorophenyl)-2-oxo-2 $\lambda^5$ -[1,3,2]-dioxaphosphonane



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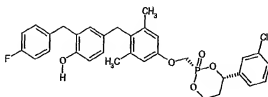
[0688]  $^1\text{H}$  NMR (400 MHz, d-DMSO):  $\delta$  9.05 (s, 1 H), 7.59 (s, 1H), 7.47-7.43 (m, 3H), 6.91 (s, 1H), 6.81 (s, 2H), 6.68-6.65 (d, 1H), 6.53-6.50 (d, 1H), 5.92-5.87 (t, 1H), 4.54-4.40 (m, 2H), 3.87 (s, 2H), 3.23-3.14 (q, 1H), 2.55-2.23 (m, 8H), 1.69 (s, 3H), 1.44 (s, 3H), 1.17-1.14 (d, 6H); LC-MS  $m/z$  = 544.8  $[\text{C}_{30}\text{H}_{36}\text{ClO}_5\text{P} + \text{H}]^+$ ; TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (1:1);  $R_f$  = 0.16; Anal. Calcd for  $(\text{C}_{30}\text{H}_{36}\text{ClO}_5\text{P} + 1.0 \text{ CH}_3\text{CO}_2\text{CH}_2\text{CH}_3)$ : C, 64.70; H, 7.03; Found: C, 64.50; H, 7.32.

**Compound 13-13-trans:** *Trans* 2-[(3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy)methyl]-4,4-dimethyl-6-(3-chlorophenyl)-2-oxo-2 $\lambda^5$ -[1,3,2]-dioxaphosphonane



[0689] LC-MS  $m/z$  = 544.8  $[\text{C}_{30}\text{H}_{36}\text{ClO}_5\text{P} + \text{H}]^+$ ;  $^1\text{H}$  NMR (400 MHz, d-DMSO):  $\delta$  9.00 (s, 1 H), 7.54 (s, 1H), 7.49-7.44 (m, 3H), 6.86 (s, 1H), 6.79 (s, 2H), 6.63-6.60 (d, 1H), 6.46-6.43 (d, 1H), 5.85-5.82 (t, 1H), 4.46-4.43 (d, 2H), 3.82 (s, 2H), 3.16-3.11 (q, 1H), 2.28-2.25 (d, 2H), 2.18 (s, 6H), 1.62 (s, 3H), 1.47 (s, 3H), 1.12-1.10 (d, 6H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (1:1);  $R_f$  = 0.27; Anal. Calcd for  $(\text{C}_{30}\text{H}_{36}\text{ClO}_5\text{P} + 1.4 \text{ CH}_3\text{CO}_2\text{CH}_2\text{CH}_3)$ : C, 64.17; H, 7.14; Found: C, 64.06; H, 6.98.

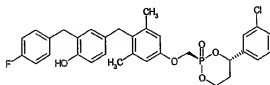
**Compound 13-14-cis:** *Cis* (*S*) 2-[(3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-hydroxybenzyl)phenoxy)methyl]-4-(3-chlorophenyl)-2-oxo-2 $\lambda^5$ -[1,3,2]-dioxaphosphonane



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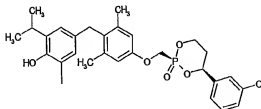
[0690] (0.041 g, 14%);  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.46(s, 1H), 7.28(m, 3H), 7.11-6.91(m, 4H), 6.63(m, 5H), 5.72(d, 1H,  $J = 11.4$  Hz), 4.71(m, 1H), 4.51(m, 3H), 3.84(m, 4H), 2.44(m, 1H), 2.22(m, 1H), 2.15(s, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexane 25% in ethyl acetate;  $R_f = 0.21$ ; LC-MS  $m/z = 582$  [ $\text{C}_{32}\text{H}_{41}\text{ClFO}_3\text{P} + \text{H}$ ] $^+$ ; Anal Calcd for ( $\text{C}_{32}\text{H}_{41}\text{ClFO}_3\text{P} + 0.5 \text{H}_2\text{O}$ ): C, 65.14; H, 5.47. Found: C, 65.31; H, 5.67.

**Compound 13-14-trans:** *Trans* (S) 2-[(3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-hydroxybenzyl)phenoxy)methyl]-4-(3-chlorophenyl)-2-oxo-2 $\lambda^5$ -[1,3,2]-dioxaphosphonane



[0691] (0.030 g, 10%);  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.46(s, 1H), 7.28(m, 3H), 7.11-6.91(m, 4H), 6.63(m, 5H), 5.86(d, 1H,  $J = 11.4$  Hz), 4.57(m, 4H), 3.84(m, 4H), 2.34(m, 1H), 2.25(m, 1H), 2.15(s, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexane 25% in ethyl acetate;  $R_f = 0.41$ ; LC-MS  $m/z = 582$  [ $\text{C}_{32}\text{H}_{41}\text{ClFO}_3\text{P} + \text{H}$ ] $^+$ ; Anal Calcd for ( $\text{C}_{32}\text{H}_{41}\text{ClFO}_3\text{P} + 0.5 \text{H}_2\text{O}$ ): C, 65.14; H, 5.47. Found: C, 65.24; H, 5.77.

**Compound 13-15-cis:** *Cis* (S)-2-[(3,5-Dimethyl-4-(5'-iodo-4'-hydroxy-3'-isopropylbenzyl)phenoxy)methyl]-4-(3-chlorophenyl)-2-oxo-2 $\lambda^5$ -[1,3,2]-dioxaphosphinane



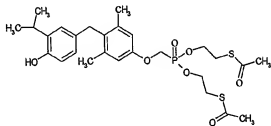
[0692] To a solution of *cis* (S)-2-[(3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)phenoxy)methyl]-4-(3-chlorophenyl)-2-oxo-2 $\lambda^5$ -[1,3,2]-dioxaphosphinane (compound 13-1-cis, 0.20 g, 0.39 mmol) in  $\text{CH}_2\text{Cl}_2$  (3.0 mL) at 0 °C was added bis(pyridine)iodonium tetrafluoroborate (0.16 g, 0.43 mmol). The reaction mixture was stirred at 0 °C for 1 h and the solvent was

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removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with 50% acetone in hexanes to afford the title compound (0.20 g, 80%) as a yellow solid: mp: 73-76 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.50 (s, 1H), 7.35 (m, 3H), 7.08 (d,  $J = 2.4$  Hz, 1H), 6.90 (d,  $J = 2.4$  Hz, 1H), 6.79 (s, 2H), 5.78 (m, 1H), 4.53-4.80 (m, 2H), 4.54 (d,  $J = 11.2$  Hz, 1H), 3.94 (s, 2H), 3.28 2.45 (m, 2H), 2.24 (s, 6H), 1.17 (d,  $J = 7.0$  Hz, 6H); LC-MS  $m/z = 641$  [ $\text{C}_{28}\text{H}_{31}\text{ClIO}_5\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{28}\text{H}_{31}\text{ClIO}_5\text{P}$ ): C, 52.48; H, 4.88. Found: C, 52.13; H, 4.52.

### Example 14

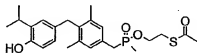
**Compound 14:** di(*S*-acetyl-2-thioethyl) [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonate



[0693] A mixture of *S*-acetyl-2-thioethanol (0.12 g, 0.96 mmol), [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonic acid (0.10 g, 0.25 mmol), pyridine (1.0 mL) and dicyclohexylcarbodiimide (0.14 g, 0.69 mmol) in DMF (2.5 mL) was heated at 70 °C for 16h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:1) to afford di(*S*-acetyl-2-thioethyl) [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonate as an oil (0.09 g, 56%): LC-MS  $m/z = 569$  [ $\text{C}_{27}\text{H}_{37}\text{O}_7\text{PS}_2 + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{27}\text{H}_{37}\text{O}_7\text{PS}_2$ ): C, 57.03; H, 6.56. Found: C, 57.02, H, 7.03; TLC conditions: Uniplat silica gel, 250 microns; mobile phase = 2/3 hexanes/EtOAc; phosphonic acid  $\text{rf} = 0.00$ ,  $\text{rf} = 0.35$ .

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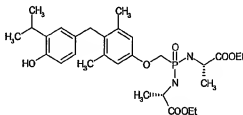
**Compound 14-2:** 2-*S*-Acetyl-thioethyl[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-methylphosphinate



[0694] The title compound was prepared from [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-methylphosphinic acid (example 72) according to the procedure described for the synthesis of Example 14. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.00 (s, 1H), 6.94 (s, 2H), 6.83 (s, 1H), 6.63 (m, 1H), 6.44 (m, 1H), 3.95 (m, 2H), 3.93 (s, 2H), 3.07 (m, 5H), 2.35 (s, 3H), 2.18 (s, 6H), 1.36 (d, *J* = 15.0 Hz, 3H), 1.10 (d, *J* = 6.0 Hz, 6H); Anal. Calcd for (C<sub>24</sub>H<sub>33</sub>O<sub>4</sub>PS + 0.7 H<sub>2</sub>O): C, 62.51; H, 7.52. Found: C, 62.25; H, 7.56. LC-MS *m/z* = 449 [C<sub>24</sub>H<sub>33</sub>O<sub>4</sub>PS-H]<sup>+</sup>; HPLC conditions: Column = Kromasil; C18-100×4.6 mm; Mobile phase = Solvent A: MeOH; Solvent B: H<sub>2</sub>O/0.05% TFA. Flow rate = 1.0 mL/min; UV@ 254 nm. Retention time in minutes. (rt = 15.08/25.00, 92% purity). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = acetone-hexanes (7:3); R<sub>f</sub> = 0.23.

### Example 15

**Compound 15-1:** di-*N*-(1-ethoxycarbonyl)ethylamino [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)]phenoxy)methylphosphonamide



[0695] To a stirred solution of [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)]phenoxy)methyl phosphonic acid (1, 0.3 g, 0.8 mmol) and DMF (0.1 mL, 0.08 mmol) in 1,2 dichloroethane (10 mL) at room temperature was added oxalylchloride (0.55 g, 2.8 mmol). The reaction mixture was heated at 50 °C for 3 h, cooled to room temperature and concentrated under

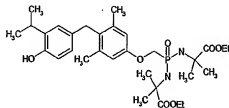


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reduced pressure. To the residue at 0 °C was added a solution of alanine ethylester (0.57 g, 4.3 mmol) and *N,N*-diisopropylethylamine (0.6 mL, 4.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub>. The reaction mixture was stirred for 14 h at room temperature and concentrated under reduced pressure. The residue was partitioned between EtOAc (50 mL) and aqueous NaHCO<sub>3</sub> solution (100 mL). The organic layer was separated, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>-MeOH (95:5) to afford Di(ethoxycarbonyl-1-ethylamino) [3,5-Dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)]phenoxy]methylphosphonamide as a yellow solid (175 mg, 52%): mp 48-50 °C; LC-MS *m/z* = 563 [C<sub>29</sub>H<sub>43</sub>N<sub>2</sub>O<sub>7</sub>P+H]<sup>+</sup>; Anal Calcd for: (C<sub>29</sub>H<sub>43</sub>N<sub>2</sub>O<sub>7</sub>P+0.2 CH<sub>2</sub>Cl<sub>2</sub>): C, 60.24; H, 7.52; N, 4.80. Found: C, 59.86; H, 8.01; N, 5.12.

[0696] Using the appropriate starting material, compounds 15-2 to 15-9 were prepared in an analogous manner to that described for the synthesis of compound 15-1.

**Compound 15-2:** di-*N*-(1-ethoxycarbonyl-1-methylethylamino)[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)]phenoxy]methylphosphonamide

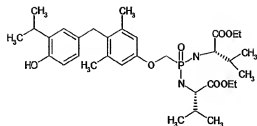


[0697] LC-MS *m/z* = 591 [C<sub>29</sub>H<sub>43</sub>N<sub>2</sub>O<sub>7</sub>P+H]<sup>+</sup>; Anal Calcd for (C<sub>29</sub>H<sub>43</sub>N<sub>2</sub>O<sub>7</sub>P+0.2 CH<sub>2</sub>Cl<sub>2</sub>): C, 60.24; H, 7.52; N, 4.80. Found: C, 59.86; H, 8.01; N, 5.12; TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate/ hexanes (4:1); R<sub>f</sub>=0.4.

[0698] Using the appropriate starting material, compound 15-3 was prepared in an analogous manner to that described for the synthesis of compound 15-1.

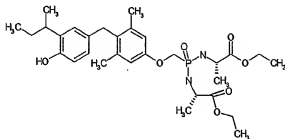
**Compound 15-3:** di-*N*-(1-ethoxycarbonyl-2-methyl-propylamino)[3,5-dimethyl-4-(3'-*iso*-propyl-4'-hydroxybenzyl)]phenoxy]methylphosphonamide

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[0699] mp: 52-55 °C; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (3:1);  $R_f$  = 0.4;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.84 (d,  $J$  = 2.1 Hz, 1 H), 6.52 (d,  $J$  = 7.2 Hz, 1 H), 6.42 (dd,  $J$  = 1.8, 4.5 Hz, 1 H), 4.02-4.20 (m, 6 H), 3.70-3.95 (m, 2 H), 3.80 (s, 2 H), 3.05-3.35 (m, 3 H), 2.13 (s, 6 H), 1.09-1.20 (m, 9 H), 0.95 (t,  $J$  = 6.9 Hz, 3 H), 0.81 (dd,  $J$  = 2.1, 6.9 Hz, 6 H); LC-MS  $m/z$  = 619  $[\text{C}_{33}\text{H}_{51}\text{N}_2\text{O}_7\text{P} + \text{H}]^+$ ; Anal Calcd for:  $(\text{C}_{33}\text{H}_{51}\text{N}_2\text{O}_7\text{P} + 0.75 \text{H}_2\text{O})$ : C, 62.29; H, 8.37; N, 4.43. Found: C, 62.48; H, 8.89; N, 4.37.

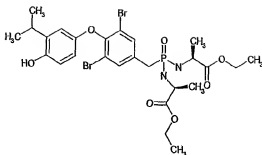
**Compound 15-4:** di-*N*-(1-ethoxycarbonylethylamino)[3,5-dimethyl-4-(4'-hydroxy-3'-*sec*-butylbenzyl)phenoxy]methylphosphonamide



[0700]  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.94 (s, 1H), 6.77 (s, 1H), 6.64-6.61 (m, 3H), 6.51-6.48 (d, 1H), 4.87-4.75 (q, 2H), 4.09-3.99 (m, 4H), 3.81 (s, 2H), 2.95-2.88 (q, 1H), 2.17 (s, 6H), 1.57-1.37 (m, 2H), 1.31-1.29 (d, 6H), 1.26-1.16 (m, 4H), 1.08-1.06 (d, 3H), 0.78-0.73 (t, 3H); LC-MS  $m/z$  = 577.6  $[\text{C}_{30}\text{H}_{45}\text{N}_2\text{O}_7\text{P} + \text{H}]^+$ ; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (1:1);  $R_f$  = 0.58; Anal. Calcd for  $(\text{C}_{30}\text{H}_{45}\text{N}_2\text{O}_7\text{P} + 1.1 \text{H}_2\text{O})$ : C, 60.41; H, 7.98; N, 4.70. Found: C, 60.12; H, 7.58; N, 4.49.

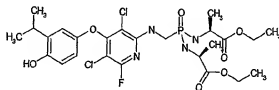
**Compound 15-5:** di-*N*-(1-ethoxycarbonylethylamino)[3,5-dibromo-4-(4'-hydroxy-3'-*iso*-propylphenyl)benzyl]phosphonamide

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[0701]  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.08 (s, 1H), 7.68 (s, 2H), 6.69-6.66 (d, 1H), 6.63 (s, 1H), 6.31-6.28 (d, 1H), 4.76-4.61 (q, 2H), 4.09-4.01 (m, 8H), 3.17-3.08 (q, 1H), 1.27-1.10 (m, 18H); LC-MS  $m/z$  = 679.4  $[\text{C}_{26}\text{H}_{35}\text{Br}_2\text{N}_2\text{O}_7\text{P} + \text{H}]^+$ ; TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = dichloromethane-ethyl acetate (1:1);  $R_f$  = 0.34; Anal. Calcd for  $(\text{C}_{26}\text{H}_{35}\text{Br}_2\text{N}_2\text{O}_7\text{P} + 0.6 \text{ CF}_3\text{CO}_2\text{H})$ : C, 43.92; H, 4.84; N, 3.78. Found: C, 43.51; H, 4.78; N, 4.26.

**Compound 15-6:** di-*N*-(1-ethoxycarbonyl-2-methyl-2-oxoethylamino)[4,6-dichloro-3-fluoro-5-(4'-hydroxy-3'-isopropylphenoxy)-pyrid-2-ylamino]methylphosphonamide

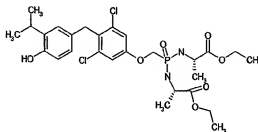


[0702] To a stirring suspension of [4,6-dichloro-3-fluoro-5-(4'-hydroxy-3'-isopropylphenoxy)-pyrid-2-ylamino]methylphosphonic (0.11 g, 0.26 mmol, US 6747048 B2) and L-alanine (0.16 g, 10.4 mmol) at room temperature in pyridine (2 mL) was added TEA (0.14 mL, 1.04 mmol), followed by a fresh prepared a solution of aldrithio-2 (0.25 g, 1.12 mmol) and  $\text{PPh}_3$  (0.29 g, 1.12 mmol) in pyridine (2 mL). The reaction mixture was stirred at 85 °C for 16 hrs. The solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate to afford the title compound as a yellow foam (40 mg, 25%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.20 (s, 1 H), 6.99 (t,  $J$  = 6.0 Hz, 1 H), 6.78 (d,  $J$  = 3.0 Hz, 1 H), 6.68 (d,  $J$  = 9.0 Hz, 1 H), 6.46 (dd,  $J$  = 3.0, 9.0 Hz, 1 H), 4.86 (m, 1 H),

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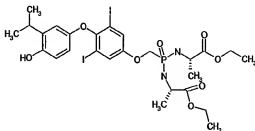
4.66 (m, 1 H), 4.07 (m, 4 H), 3.83 (m, 2 H), 3.44 (m, 2 H), 3.16 (m, 1 H), 1.11 – 1.27 (m, 18 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate;  $R_f = 0.54$ ; LC-MS  $m/z = 624$  [ $C_{25}H_{34}Cl_2FN_4O_7P + H$ ] $^+$ ; Anal. Calcd for ( $C_{25}H_{34}Cl_2FN_4O_7P$ ): C, 48.16; H, 5.50; N, 8.99. Found: C, 47.99; H, 5.26; N, 8.77.

**Compound 15-7:** Di-*N*-(*l*-1-ethoxycarbonylethylamino)[3,5-dichloro-4-(4'-hydroxy-3'-*iso*-propylbenzyl)]phenoxy]methylphosphonamide



[0703]  $^1H$  NMR (300 MHz,  $DMSO-d_6$ ):  $\delta$  9.11 (s, 1 H), 7.12 (s, 2 H), 6.97 (m, 1 H), 6.66 (m, 2 H), 4.89 (m, 2 H), 4.22 (m, 2 H), 4.05-3.93 (m, 8 H), 3.14 (m, 1 H), 1.28 (m, 6 H), 1.16 (m, 12 H); LC-MS  $m/z = 603$  [ $C_{27}H_{33}Cl_2N_2O_7P + H$ ] $^+$ ; Anal. Calcd for ( $C_{27}H_{33}Cl_2N_2O_7P + 0.5 H_2O$ ): C, 52.95; H, 6.25; N, 4.57. Found: C, 52.97; H, 6.32; N, 4.71; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (4:1);  $R_f = 0.26$ .

**Compound 15-8:** Di-*N*-(*l*-1-ethoxycarbonylethylamino)[3,5-diiodo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)]phenoxy]methylphosphonamide

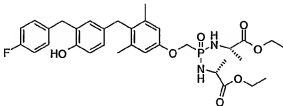


[0704]  $^1H$  NMR (300 MHz,  $DMSO-d_6$ ):  $\delta$  8.99 (s, 1 H), 7.50 (s, 2 H), 6.68 (m, 1 H), 6.56 (m, 1 H), 6.25 (m, 1 H), 4.87 (m, 2 H), 4.18 (m, 2 H), 4.06-3.95 (m, 6 H), 3.17 (m, 1 H), 1.32 (m, 6 H), 1.21-1.11 (m, 12 H); LC-MS  $m/z = 789$  [ $C_{26}H_{35}I_2N_2O_8P + H$ ] $^+$ ; Anal. Calcd for ( $C_{26}H_{35}I_2N_2O_8P + 0.1 H_2O$ ): C, 39.52;

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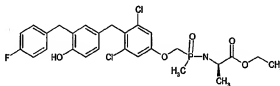
H, 4.49; N, 3.55. Found: C, 39.49; H, 4.50; N, 3.46; TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = acetone-hexanes (1:1);  $R_f$  = 0.13.

**Compound 15-9:** Di-*N*-(*l*-1-ethoxycarbonylethylamino)[3,5-dimethyl-4-(3'-  
(4-fluorobenzyl)-4'-hydroxybenzyl)]phenoxy)methylphosphonamide



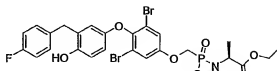
[0705]  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.12(m, 2H), 7.89(m, 2H), 6.61(m, 5H), 4.19(dd, 2H,  $J$  = 2.4 Hz and  $J$  = 14 Hz), 4.08(m, 5H), 3.84(s, 2H), 3.81(s, 2H), 2.15(s, 6H), 2.25(m, 1H), 2.15(s, 6H), 1.40(d, 6H,  $J$  = 7.5 Hz), 1.21(m, 6H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate;  $R_f$  = 0.18; LC-MS  $m/z$  = 629 [ $\text{C}_{33}\text{H}_{42}\text{FN}_2\text{O}_7\text{P} + \text{H}$ ] $^+$ , Anal Calcd for ( $\text{C}_{33}\text{H}_{42}\text{FN}_2\text{O}_7\text{P} + 1.1 \text{ H}_2\text{O}$ ): C, 61.12; H, 6.87, N, 4.32. Found: C, 60.85; H, 6.78, N, 4.72.

**Compound 15-10:** *N*-(*l*-1-ethoxycarbonylethylamino)[3,5-dichloro-4-(3'-  
(4-fluorobenzyl)-4'-hydroxybenzyl)]phenoxymethyl)methylphosphinamide



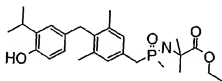
[0706]  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.11(m, 4H), 6.92(t, 2H),  $J$  = 8.7 Hz), 6.76(m, 2H), 6.63(d, 1H),  $J$  = 8 Hz), 4.26(d, 2H),  $J$  = 7.8 Hz), 4.12(m, 3H), 3.98(m, 2H), 3.83(s, 2H), 1.58(m, 3H), 1.38(m, 3H); TLC conditions: Uniplate silica gel, 250 microns; ethyl acetate-methanol [20:1];  $R_f$  = 0.2; LC-MS  $m/z$  568 [ $\text{C}_{27}\text{H}_{29}\text{Cl}_2\text{FNO}_5\text{P} + \text{H}$ ] $^+$ ; Anal Calcd for ( $\text{C}_{27}\text{H}_{29}\text{Cl}_2\text{FNO}_5\text{P}$ ): C, 56.27; H, 5.34; N, 2.40 Found: C, 56.17; H, 5.71; N, 2.62.

**Compound 15-11:** Methyl *N*-(*l*-1-ethoxycarbonylethylamino) [3,5-dibromo-4-  
(3'--(4-fluorobenzyl)-4'-hydroxyphenoxy)methylphosphonamide



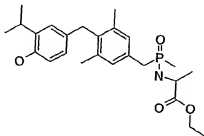
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[0707]  $^1\text{H}$  NMR (200 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.12 (s, 2H), 7.18 (m, 2H), 7.94 (t,  $J = 8$  Hz, 2H), 6.70 (d,  $J = 8.8$  Hz, 1H), 4.33 (m, 2H), 4.08 (m, 1H), 3.83 (s, 2H), 3.77 (m, 3H), 1.41 (m, 3H), 1.27 (m, 3H); TLC conditions: Uniplate silica gel, 250 microns; ethyl acetate;  $R_f = 0.30$ ; LC-MS  $m/z$  676 [ $\text{C}_{26}\text{H}_{27}\text{Br}_2\text{FO}_7\text{P} + \text{H}$ ] $^+$ .  
**Compound 15-12:** *N*-(1-ethoxycarbonyl-1-methylethylamino)[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-methylphosphinamide



[0708] The title compound was prepared from [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-methylphosphinic acid (example 72) according to the procedure described for the synthesis of Example 15-2. MP: 62-65 °C  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.02 (s, 2H), 6.84 (s, 1H), 6.59 (m, 2H), 4.21 (m, 2H), 3.96 (s, 2H), 3.22 (m, 1H), 3.12 (m, 2H), 2.24 (s, 6H), 1.52 (s, 6H), 1.43 (d,  $J = 16.5$  Hz, 3H), 1.30 (m, 3H), 1.14 (d,  $J = 6.0$  Hz, 6H); Anal. Calcd for ( $\text{C}_{26}\text{H}_{38}\text{NO}_4\text{P}$ ): C, 67.95; H, 8.33; N, 3.05. Found: C, 67.69; H, 8.39; N, 2.93. LC-MS  $m/z = 460$  [ $\text{C}_{26}\text{H}_{38}\text{NO}_4\text{P} + \text{H}$ ] $^+$ ; HPLC conditions: Column = Kromasil; C18-100 $\times$ 4.6 mm; Mobile phase = Solvent A: MeOH; Solvent B:  $\text{H}_2\text{O}/0.05\%$  TFA. Flow rate = 1.0 mL/min; UV@ 280 nm. Retention time in minutes. (rt = 15.12/25.00, 93% purity). TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = acetone-hexanes (7:3);  $R_f = 0.31$ .

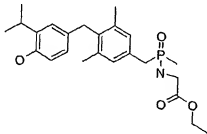
**Compound 15-13:** *N*-(*L*-Ethoxycarbonyl-1-ethylamino)[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-methylphosphinamide



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[0709] The title compound was prepared from [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-methylphosphinic acid (example 72) according to the procedure described for the synthesis of compound 15-1 as a light yellow foam:  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.00 (s, 1H), 6.92 (s, 2H), 6.84 (s, 1H), 6.62 (d,  $J = 8.1$  Hz, 1H), 6.47 (d,  $J = 8.1$  Hz, 1H), 4.67 (m, 1H), 4.07 (m, 2H), 3.85 (s, 2H), 3.75 (m, 1H), 3.14 (m, 1H), 2.85 (d,  $J = 17.1$  Hz, 2H), 2.17 (s, 6H), 1.21 (m, 9H), 1.10 (d,  $J = 6.9$  Hz, 6H); LC-MS  $m/z = 446$  [ $\text{C}_{25}\text{H}_{36}\text{NO}_4\text{P} + \text{H}$ ] $^+$ ; HPLC conditions: Column = kromasil C18,  $4.6 \times 100$  mm  $5\mu$ ; Mobile phase: from 30 to 50% MeOH in water with 0.05% TFA in 15 min. Flow rate = 1.0 mL/min; UV@ 280 nm. Retention time in minutes (rt = 14.54/25 min, 99% purity). Anal. Calcd for ( $\text{C}_{25}\text{H}_{36}\text{NO}_4\text{P} + 0.4\text{H}_2\text{O}$ ): C, 66.32; H, 8.19; N, 3.09. Found: C, 66.69; H, 8.64; N, 2.93.

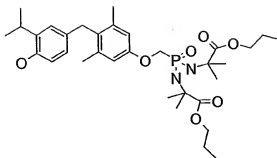
**Compound 15-14:** *N*-(Ethoxycarbonyl-methylamino)[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-methylphosphinamide



[0710] The title compound was prepared from [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-methylphosphinic acid (example 72) according to the procedure described for the synthesis of compound 15-1 as a white solid:  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.00 (s, 1H), 6.94 (s, 2H), 6.84 (s, 1H), 6.62 (d,  $J = 8.1$  Hz, 1H), 6.47 (d,  $J = 8.1$  Hz, 1H), 4.57 (m, 1H), 4.07 (m, 2H), 3.85 (s, 2H), 3.55 (m, 2H), 3.15 (m, 1H), 2.98 (d,  $J = 16.8$  Hz, 2H), 2.17 (s, 6H), 1.21 (m, 6H), 1.10 (d,  $J = 6.9$  Hz, 6H); MP: 176-178  $^{\circ}\text{C}$ ; LC-MS  $m/z = 432$  [ $\text{C}_{24}\text{H}_{34}\text{NO}_4\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{24}\text{H}_{34}\text{NO}_4\text{P} + 0.3\text{H}_2\text{O}$ ): C, 65.98; H, 7.98; N, 3.21. Found: C, 65.84; H, 7.81; N, 3.22.

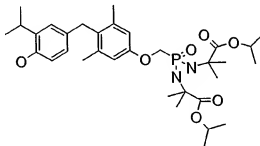
**Compound 15-15:** Di-*N*-(1-propylcarbonyl-1-methylethylamino)[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-phosphonamide

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[0711] The title compound was prepared from compound 7 according to the procedure described for the synthesis of compound 15-1, as a white foam:  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.00 (s, 1H), 6.84 (s, 1H), 6.69 (s, 2H), 6.62 (d,  $J = 7.8$  Hz, 1H), 6.47 (d,  $J = 7.8$  Hz, 1H), 4.58 (d,  $J = 11.1$  Hz, 2H), 4.00 (m, 6H), 3.81 (s, 2H), 3.14 (m, 1H), 2.18 (s, 6H), 1.62 (m, 4H), 1.47 (d,  $J = 13.5$  Hz, 12H), 1.11 (d,  $J = 6.9$  Hz, 6H), 0.91 (m, 6H); LC-MS  $m/z = 619$  [ $\text{C}_{35}\text{H}_{55}\text{N}_2\text{O}_7\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{35}\text{H}_{55}\text{N}_2\text{O}_7\text{P} + 0.5 \text{CH}_2\text{Cl}_2$ ): C, 60.85; H, 7.93; N, 4.24. Found: C, 60.72; H, 7.83; N, 4.16.

**Compound 15-16:** Di-*N*-(*l*-isopropylcarbonyl-1-methylethylamino)[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-phosphonamide

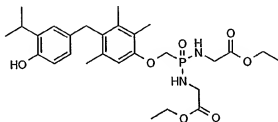


[0712] The title compound was prepared from compound 7 according to the procedure described for the synthesis of compound 15-1, as a white foam:  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.00 (s, 1H), 6.85 (s, 1H), 6.69 (s, 2H), 6.62 (d,  $J = 8.1$  Hz, 1H), 6.47 (d,  $J = 8.1$  Hz, 1H), 4.89 (m, 2H), 4.54 (d,  $J = 10.8$  Hz, 2H), 4.05 (d,  $J = 10.8$  Hz, 2H), 3.81 (s, 2H), 3.11 (m, 1H), 2.18 (s, 6H), 1.45 (d,  $J = 16.5$  Hz, 12H), 1.21 (m, 12H), 1.11 (d,  $J = 6.9$  Hz, 6H); LC-MS  $m/z = 619$  [ $\text{C}_{35}\text{H}_{55}\text{N}_2\text{O}_7\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{35}\text{H}_{55}\text{N}_2\text{O}_7\text{P} + 0.4 \text{H}_2\text{O}$ ): C, 63.32; H, 8.34; N, 4.48. Found: C, 63.36; H, 8.64; N, 4.44.



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**Compound 15-17:** Di-*N*-(*L*-ethoxycarbonyl-methylamino)[4-(4'-hydroxy-3'-isopropylbenzyl)-2,3,5-trimethylphenoxy-methyl]phosphonamide



Step a:

[0713] A solution consisting of [4-(4'-hydroxy-3'-isopropylbenzyl)-2,3,5-trimethylphenoxy-methyl]phosphonic acid (compound 61, 1.2 g, 3.1 mmol) and acetic anhydride (2 mL) in toluene (5 mL) was refluxed overnight. The volatiles were removed under vacuum and to the oily residue was added THF (3 mL) and H<sub>2</sub>O (1 mL). The mixture was stirred at rt for 5 hrs before being concentrated under vacuum. Co-evaporation of the residue with toluene afforded [4-(4'-acetoxy-3'-isopropylbenzyl)-2,3,5-trimethylphenoxy-methyl]-phosphonic acid as an off-white foam. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.11 (d, *J* = 2.1 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.79 (s, 1H), 6.65 (dd, *J* = 8.4 Hz and 2.1 Hz, 1H), 4.04 (d, *J* = 10.5 Hz, 2H), 3.96 (s, 2H), 2.96-2.87 (m, 1H), 2.27 (s, 3H), 2.20 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H), 1.10 (d, *J* = 7.8 Hz, 6H); <sup>31</sup>P NMR (DMSO-*d*<sub>6</sub>) δ 15.32 (s); LC-MS *m/z* = 419 [C<sub>22</sub>H<sub>29</sub>O<sub>6</sub>P-H]<sup>+</sup>.

Step b:

[0714] A solution consisting of [4-(4'-acetoxy-3'-isopropylbenzyl)-2,3,5-trimethylphenoxy-methyl]phosphonic acid (216 mg, 0.51 mmol), oxalyl chloride (0.18 mL, 2.1 mmol) and DMF (1 drop) in dichloroethane (15 mL) was heated at 50 °C for 2 hrs. The reaction mixture was then concentrated under vacuum and the oil residue dissolved in dichloromethane. After cooling to 0 °C, ethyl glycine as a 5 M solution in dichloromethane (0.41 mL, 2.1 mmol) and Hunigs base (0.35 mmol, 2.1 mmol) were added. The resulting solution was allowed to reach rt overnight. The reaction mixture was washed with a pH 7 phosphate buffer solution, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated

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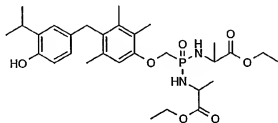
under vacuum to afford a dark amber-colored oil which was purified by preparative TLC (2mm, SiO<sub>2</sub>) using ethyl acetate/hexane (9:1) as eluant. Evaporation of the solvent gave {*l*-ethoxycarbonyl-methylamino}-[4-(4'-acetoxy-3'-isopropylbenzyl)-2,3,5-trimethylphenoxyethyl]phosphonamide as an amber oil (174 mg, 57%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.01 (s, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.61 (s, 1H), 4.27 (d, *J* = 9.6 Hz, 2H), 4.20-4.08 (m, 4H), 3.99 (s, 2H), 3.96-3.74 (m, 4H), 3.00-2.91 (m, 1H), 2.29 (s, 3H), 2.23 (s, 3H), 2.19 (s, 3H), 2.12 (s, 3H), 1.28-1.22 (m, 6H), 1.16 (d, *J* = 6.6 Hz, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 22.63 (s); LC-MS *m/z* = 591 [C<sub>30</sub>H<sub>43</sub>N<sub>2</sub>O<sub>8</sub>P + H]<sup>+</sup>; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate; R<sub>f</sub> = 0.47.

## Step c:

[0715] A solution of {*l*-Ethoxycarbonyl-methylamino}-[4-(4'-acetoxy-3'-isopropylbenzyl)-2,3,5-trimethylphenoxyethyl]phosphonamide (174 mg, 0.30 mmol) and anhydrous hydrazine (0.03 mL, 0.84 mmol) in *t*-BuOH (3 mL) was heated at 30 °C for 48 hrs. The mixture was concentrated under vacuum and the residue dissolved in ethyl acetate. After washing with a solution of H<sub>2</sub>O/AcOH (5:1), the organic portion was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum to afford crude product which was purified by preparative TLC (2mm, SiO<sub>2</sub>) using dichloromethane/methanol (20:1) as eluant. Evaporation of the solvent gave the title compound as an amber oil (64 mg, 40%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.96 (s, 1H), 6.85 (s, 1H), 6.70 (s, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 6.43 (d, *J* = 8.4 Hz, 1H), 4.83 (t, *J* = 10.5 Hz, 1H), 4.70 (t, *J* = 10.5 Hz, 1H), 4.08-3.90 (m, 8H), 3.83 (s, 2H), 3.17-3.08 (m, 1H), 2.19 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 1.29 (d, *J* = 6.9 Hz, 6H), 1.17-1.09 (m, 6H); <sup>31</sup>P NMR (DMSO-*d*<sub>6</sub>) δ 21.56 (s); LC-MS *m/z* = 549 [C<sub>28</sub>H<sub>41</sub>N<sub>2</sub>O<sub>7</sub>P + H]<sup>+</sup>; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = dichloromethane/methanol (10:1); R<sub>f</sub> = 0.42; Anal. Calcd for (C<sub>28</sub>H<sub>41</sub>N<sub>2</sub>O<sub>7</sub>P + 0.2 H<sub>2</sub>O): C, 60.90; H, 7.56; N, 5.07. Found: C, 60.95, H, 7.63; N, 5.21.

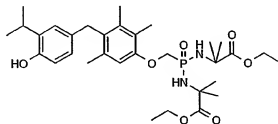
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**Compound 15-18:** Di-*N*-{*l*-1-ethoxycarbonyl-ethylamino}-[4-(4'-hydroxy-3'-isopropylbenzyl)-2,3,5-trimethylphenoxyethyl]phosphonamide



[0716] The title compound was prepared from [4-(4'-acetoxy-3'-isopropylbenzyl)-2,3,5-trimethylphenoxyethyl]phosphonic acid (compound 15-17, step b) according to the procedure described for the synthesis of compound 15-17, step c as an amber-colored oil (51%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.96 (s, 1H), 6.85 (s, 1H), 6.70 (s, 1H), 6.59 (d,  $J = 8.4$  Hz, 1H), 6.43 (d,  $J = 8.4$  Hz, 1H), 4.83 (t,  $J = 10.5$  Hz, 1H), 4.70 (t,  $J = 10.5$  Hz, 1H), 4.08-3.90 (m, 8H), 3.83 (s, 2H), 3.17-3.08 (m, 1H), 2.19 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 1.29 (d,  $J = 6.9$  Hz, 6H), 1.17-1.12 (m, 6H), 1.10 (d,  $J = 7.2$  Hz, 6H);  $^{31}\text{P}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  19.33 (s); LC-MS  $m/z = 577$  [ $\text{C}_{30}\text{H}_{45}\text{N}_2\text{O}_7\text{P} + \text{H}$ ] $^+$ ; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = dichloromethane/methanol (10:1);  $R_f = 0.47$ ; Anal. Calcd for ( $\text{C}_{30}\text{H}_{45}\text{N}_2\text{O}_7\text{P} + 0.5 \text{H}_2\text{O}$ ): C, 61.52; H, 7.92; N, 4.78. Found: C, 61.75; H, 8.02; N, 5.02.

**Compound 15-19:** Di-*N*-{*l*-1-ethoxycarbonyl-1-methylethylamino}[4-(4'-hydroxy-3'-isopropylbenzyl)-2,3,5-trimethylphenoxyethyl]phosphonamide



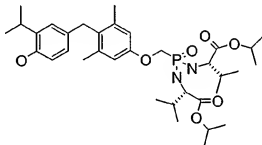
Step b:

[0717] The title compound was prepared from [4-(4'-acetoxy-3'-isopropylbenzyl)-2,3,5-trimethylphenoxyethyl]phosphonic acid (compound 15-17, step b) according to the procedure described for the synthesis of

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compound 15-17, step c as an amber-colored oil (62%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.96 (s, 1H), 6.85 (s, 1H), 6.70 (s, 1H), 6.59 (d,  $J = 8.4$  Hz, 1H), 6.43 (d,  $J = 8.4$  Hz, 1H), 4.56 (d,  $J = 10.8$  Hz, 2H), 4.13-4.00 (m, 6H), 3.83 (s, 2H), 3.17-3.08 (m, 1H), 2.19 (s, 3H), 2.14 (s, 3H), 2.08 (s, 3H), 1.49 (s, 6H), 1.42 (s, 6H), 1.19 (t,  $J = 7.2$  Hz, 6H), 1.10 (d,  $J = 6.9$  Hz, 6H);  $^{31}\text{P}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  16.97 (s); LC-MS  $m/z = 606$  [ $\text{C}_{32}\text{H}_{49}\text{N}_2\text{O}_7\text{P} + \text{H}$ ] $^+$ ; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = dichloromethane/methanol (10:1);  $R_f = 0.54$ ; Anal. Calcd for ( $\text{C}_{32}\text{H}_{49}\text{N}_2\text{O}_7\text{P}$ ): C, 63.56; H, 8.17; N, 4.63. Found: C, 63.58, H, 7.97; N, 4.45.

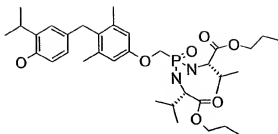
**Compound 15-20:** Di-*N*-(*l*-1-ethoxycarbonyl-2-methyl-propylamino)[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonamide



[0718] The title compound was prepared from [3,5-dimethyl-4-(3'-*iso*-propyl-4'-hydroxybenzyl)phenoxy]methylphosphonic acid (compound 7) according to the procedure described for the synthesis of compound 15-1 as a white foam:  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.00 (s, 1H), 6.82 (s, 1H), 6.63 (s, 2H), 6.61 (d,  $J = 8.1$  Hz, 1H), 6.47 (d,  $J = 8.1$  Hz, 1H), 4.87 (m, 2H), 4.54 (m, 1H), 4.12 (m, 3H), 3.82 (s, 2H), 3.68 (m, 2H), 3.14 (m, 1H), 2.17 (s, 6H), 1.98 (m, 2H), 1.23 (d,  $J = 6.3$  Hz, 6H), 1.12 (m, 12H), 0.89 (m, 12H); LC-MS  $m/z = 647$  [ $\text{C}_{35}\text{H}_{55}\text{N}_2\text{O}_7\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{35}\text{H}_{55}\text{N}_2\text{O}_7\text{P} + 0.3\text{H}_2\text{O}$ ): C, 64.46; H, 8.59; N, 4.30. Found: C, 64.29; H, 8.49; N, 4.13.

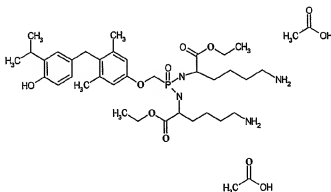
**Compound 15-21:** Di-*N*-(*l*-1-propyloxycarbonyl-2-methyl-propylamino)[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonamide

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[0719] The title compound was prepared from [3,5-dimethyl-4-(3'-*iso*-propyl-4'-hydroxybenzyl)phenoxy]methylphosphonic acid (compound 7) according to the procedure described for the synthesis of compound 15-1 as a white foam:  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.00 (s, 1H), 6.83 (d,  $J = 2.1$  Hz, 1H), 6.61 (m, 3H), 6.47 (dd,  $J = 8.1, 2.1$  Hz, 1H), 4.57 (t,  $J = 8.7$  Hz, 1H), 4.24 (t,  $J = 8.7$  Hz, 1H), 3.92 (m, 6H), 3.81 (s, 2H), 3.68 (m, 2H), 3.14 (m, 1H), 2.17 (s, 6H), 1.98 (m, 2H), 1.57 (m, 4H), 1.11 (d,  $J = 6.9$  Hz, 6H), 0.89 (m, 18H); LC-MS  $m/z = 647$  [ $\text{C}_{35}\text{H}_{55}\text{N}_2\text{O}_7\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{35}\text{H}_{55}\text{N}_2\text{O}_7\text{P}$ ): C, 64.99; H, 8.57; N, 4.33. Found: C, 64.60; H, 8.78; N, 4.39.

**Compound 15-22:** Di-*N*-(*l*-1-ethoxycarbonyl-1-(5-pentylamino))([3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methyl)phosphonamide acetic acid salt

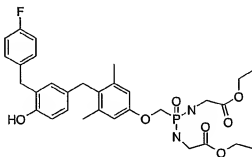


[0720] The title compound was prepared from [3,5-dimethyl-4-(3'-*iso*-propyl-4'-hydroxybenzyl)phenoxy]methylphosphonic acid (compound 7) according to the procedure described for the synthesis of compound 15-1 as a white foam:  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  6.83 (d,  $J = 2.1$  Hz, 1H), 6.61 (m, 3H), 6.47 (dd,  $J = 8.1, 2.1$  Hz, 1H), 4.77 (t,  $J = 8.7$  Hz, 1H), 4.61 (t,  $J = 8.7$  Hz, 1H), 4.02 (m, 6H), 3.81 (s, 4H), 3.14 (m, 1H), 2.58 (m, 4H), 2.17 (s, 6H),

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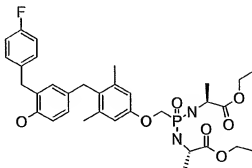
1.83 (s, 6H), 1.61 (m, 4H), 1.38 (m, 8H), 1.11 (m, 12H); LC-MS  $m/z$  = 677 [ $C_{35}H_{57}N_4O_7P + H$ ] $^+$ ; Anal. Calcd for ( $C_{35}H_{57}N_4O_7P + 2AcOH + 0.2EtOH + 1.5H_2O$ ): C, 56.80; H, 8.37; N, 6.72. Found: C, 56.51; H, 8.07; N, 7.04.

**Compound 15-23:** Di-*N*-(ethoxycarbonyl-methylamino)[3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-hydroxybenzyl)phenoxy]methylphosphonamide



[0721] The title compound was prepared from [3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-hydroxybenzyl)phenoxy]methylphosphonic acid (compound 40) according to the procedure described for the synthesis of compound 15-17 as a white foam:  $^1H$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  9.17 (s, 1H), 7.11 (m, 4H), 6.64 (m, 5H), 4.77 (m, 2H), 4.06 (m, 6H), 3.77 (s, 4H), 3.66 (s, 4H), 2.14 (s, 6H), 1.17 (t,  $J$  = 6.9 Hz, 6H); LC-MS  $m/z$  = 601 [ $C_{31}H_{38}FN_2O_7P + H$ ] $^+$ ; Anal. Calcd for ( $C_{31}H_{38}FN_2O_7P + 0.3H_2O$ ): C, 61.44; H, 6.42; N, 4.62. Found: C, 61.14; H, 6.10; N, 4.48.

**Compound 15-24:** Di-*N*-(1-ethoxycarbonyl-ethylamino)[3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-hydroxybenzyl)phenoxy]methylphosphonamide

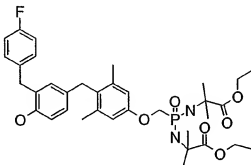


[0722] The title compound was prepared from [3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-hydroxybenzyl)phenoxy]methylphosphonic acid (compound 40) according to the procedure described for the synthesis of compound 15-17

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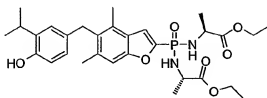
as a white foam:  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.17 (s, 1H), 7.11 (m, 4H), 6.64 (m, 5H), 4.77 (m, 2H), 4.06 (m, 8H), 3.77 (s, 4H), 2.14 (s, 6H), 1.26 (d,  $J = 6.9$  Hz, 6H), 1.14 (m, 6H); LC-MS  $m/z = 629$  [ $\text{C}_{33}\text{H}_{42}\text{FN}_2\text{O}_7\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{33}\text{H}_{42}\text{FN}_2\text{O}_7\text{P}$ ): C, 63.05; H, 6.73; N, 4.46. Found: C, 62.77; H, 6.50; N, 4.26.

**Compound 15-25:** Di-*N*-(*l*-1-ethoxycarbonyl-1-methyl-ethylamino)[3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-hydroxybenzyl)phenoxy]methylphosphonamide



[0723] The title compound was prepared from [3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-hydroxybenzyl)phenoxy]methylphosphonic acid (compound 40) according to the procedure described for the synthesis of compound 15-17 as a white foam:  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.17 (s, 1H), 7.11 (m, 4H), 6.64 (m, 5H), 4.57 (d,  $J = 7.2$  Hz, 2H), 4.06 (m, 6H), 3.74 (s, 4H), 2.11 (s, 6H), 1.44 (s, 6H), 1.40 (s, 6H), 1.16 (d,  $J = 6.9$  Hz, 6H); LC-MS  $m/z = 657$  [ $\text{C}_{35}\text{H}_{46}\text{FN}_2\text{O}_7\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{35}\text{H}_{46}\text{FN}_2\text{O}_7\text{P} + 0.5\text{TFA}$ ): C, 60.58; H, 6.57; N, 3.92. Found: C, 60.28; H, 6.24; N, 3.68.

**Compound 15-26:** Di-*N*-(*l*-1-ethoxycarbonyl-1-ethylamino)-4,6-dimethyl-5-(4'-hydroxy-3'-isopropylbenzyl)benzofuran-2-phosphonamide

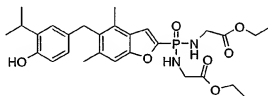


[0724] The title compound was prepared from 4,6-dimethyl-5-(4'-hydroxy-3'-isopropylbenzyl)benzofuran-2-phosphonic acid (Example 45) according to the

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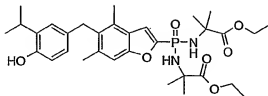
procedure described for the synthesis of Example 15-1. MP: 66-69 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.52 (d, *J* = 2.1 Hz, 1H), 7.28 (s, 1H), 6.84 (d, *J* = 2.1 Hz, 1H), 6.56 (m, 2H), 4.08 (m, 8H), 3.20 (m, 1H), 2.46 (s, 3H), 2.37 (s, 3H), 1.42 (m, 6H), 1.24 (t, *J* = 6.9 Hz, 3H), 1.15 (m, 9H); LC-MS *m/z* = 573 [C<sub>30</sub>H<sub>41</sub>N<sub>2</sub>O<sub>7</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>30</sub>H<sub>41</sub>N<sub>2</sub>O<sub>7</sub>P): C, 62.92; H, 7.22; N, 4.89. Found: C, 62.98; H, 7.26; N, 4.71.

**Compound 15-27:** Di-*N*-(ethoxycarbonyl-methylamino)-4,6-dimethyl-5-(4'-hydroxy-3'-isopropylbenzyl)benzofuran-2-phosphonamide



[0725] The title compound was prepared from 4,6-dimethyl-5-(4'-hydroxy-3'-isopropylbenzyl)benzofuran-2-phosphonic acid (Example 45) according to the procedure described for the synthesis of Example 15-1. MP: 58-61 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.56 (d, *J* = 2.1 Hz, 1H), 7.28 (s, 1H), 6.84 (d, *J* = 2.1 Hz, 1H), 6.56 (m, 2H), 4.17 (q, *J* = 6.9 Hz, 4H), 4.08 (s, 2H), 3.83 (m, 4H), 3.22 (m, 1H), 2.47 (s, 3H), 2.37 (s, 3H), 1.24 (m, 6H), 1.14 (d, *J* = 7.1 Hz, 6H); LC-MS *m/z* = 545 [C<sub>28</sub>H<sub>37</sub>N<sub>2</sub>O<sub>7</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>28</sub>H<sub>37</sub>N<sub>2</sub>O<sub>7</sub>P): C, 61.76; H, 6.85; N, 5.14. Found: C, 61.47; H, 6.88; N, 5.01.

**Compound 15-28:** Di-*N*-(*l*-1-ethoxycarbonyl-1-methyl-1-ethylamino)-4,6-dimethyl-5-(4'-hydroxy-3'-isopropylbenzyl)benzofuran-2-phosphonamide



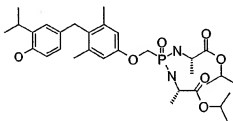
[0726] The title compound was prepared from 4,6-dimethyl-5-(4'-hydroxy-3'-isopropylbenzyl)benzofuran-2-phosphonic acid (Example 45) according to the procedure described for the synthesis of Example 15-1. MP: 50-53 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.45 (d, *J* = 2.1 Hz, 1H), 7.30 (s, 1H), 6.84 (d, *J*



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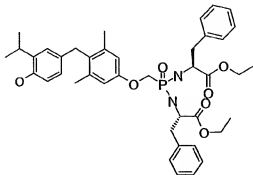
= 2.1 Hz, 1H), 6.56 (m, 2H), 4.17 (q,  $J = 6.9$  Hz, 4H), 4.10 (s, 2H), 3.22 (m, 1H), 2.47 (s, 3H), 2.37 (s, 3H), 1.60 (s, 6H), 1.49 (s, 6H), 1.24 (t,  $J = 6.9$  Hz, 6H), 1.14 (d,  $J = 7.1$  Hz, 6H); LC-MS  $m/z = 601$  [ $C_{32}H_{45}N_2O_7P + H$ ] $^+$ ; Anal. Calcd for ( $C_{32}H_{45}N_2O_7P + 0.7 H_2O$ ): C, 62.67; H, 7.63; N, 4.57. Found: C, 62.40; H, 7.90; N, 4.79.

**Example 15-29:** Di-*N*-(*l*-1-isopropoxycarbonyl-ethylamino)[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonamide



[0727] The title compound was prepared from [3,5-dimethyl-4-(3'-*iso*-propyl-4'-hydroxybenzyl)phenoxy]methylphosphonic acid (compound 7) according to the procedure described for the synthesis of compound 15-1 as a white foam. MP 55-58 °C;  $^1H$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  8.99 (s, 1H), 6.84 (s, 1H), 6.63 (m, 3H), 6.48 (m, 1H), 4.87-4.71 (m, 4H), 4.06 (d,  $J = 15.0$  Hz, 2H), 3.88 (m, 2H), 3.81 (s, 2H), 3.20 (m, 1H), 2.17 (s, 6H), 1.30 (m, 6H), 1.20-1.09 (m, 18H); LC-MS  $m/z = 591$  [ $C_{31}H_{47}N_2O_7P + H$ ] $^+$ ; Anal. Calcd for ( $C_{31}H_{47}N_2O_7P + 0.4 H_2O$ ): C, 62.27; H, 8.06; N, 4.69. Found: C, 62.24; H, 7.99; N, 4.76; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = acetone-hexanes (2:5);  $R_f = 0.33$ .

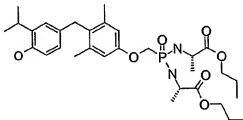
**Example 15-30:** Di-*N*-(*l*-1-ethoxycarbonyl-2-phenylethylamino)-[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonamide



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[0728] The title compound was prepared from [3,5-dimethyl-4-(3'-*iso*-propyl-4'-hydroxybenzyl)phenoxy]methylphosphonic acid (compound 7) according to the procedure described for the synthesis of compound 15-1 as a white foam. MP 60-63 °C;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  9.00 (s, 1H), 7.30-7.15 (m, 10H), 6.84 (s, 1H), 6.64 (m, 1H), 6.50 (m, 3H), 4.75 (m, 1H), 4.38 (m, 1H), 4.00 (m, 6H), 3.95 (s, 2H), 3.65 (d,  $J$  = 15.0 Hz, 2H), 3.20 (m, 1H), 2.95 (m, 5H), 2.15 (s, 6H), 1.12 (m, 12H); LC-MS  $m/z$  = 715 [ $\text{C}_{41}\text{H}_{51}\text{N}_2\text{O}_7\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{41}\text{H}_{51}\text{N}_2\text{O}_7\text{P} + 0.4 \text{H}_2\text{O}$ ): C, 68.20; H, 7.23; N, 3.88. Found: C, 68.16; H, 7.26; N, 3.86; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = acetone-hexanes (2:5);  $R_f$  = 0.35.

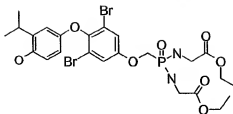
**Example 15-31:** Di-*N*-(1-propyloxycarbonyl-ethylamino)[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonamide



[0729] The title compound was prepared from [3,5-dimethyl-4-(3'-*iso*-propyl-4'-hydroxybenzyl)phenoxy]methylphosphonic acid (compound 7) according to the procedure described for the synthesis of compound 15-1 as a white foam.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  8.99 (s, 1H), 6.83 (s, 1H), 6.63 (m, 3H), 6.48 (m, 1H), 4.83-4.75 (m, 2H), 4.08 (d,  $J$  = 15.0 Hz, 2H), 3.99-3.94 (m, 6H), 3.81 (s, 2H), 3.18 (m, 1H), 2.17 (s, 6H), 1.55 (m, 4H), 1.29 (d,  $J$  = 6.0 Hz, 2H), 1.11 (d,  $J$  = 7.0 Hz, 2H), 0.88 (m, 6H); LC-MS  $m/z$  = 591 [ $\text{C}_{31}\text{H}_{47}\text{N}_2\text{O}_7\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{31}\text{H}_{47}\text{N}_2\text{O}_7\text{P} + 0.3 \text{H}_2\text{O}$ ): C, 62.46; H, 8.05; N, 4.70. Found: C, 62.44; H, 7.95; N, 4.73; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = acetone-hexanes (2:5);  $R_f$  = 0.13.

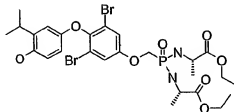
**Example 15-32:** Di-*N*-(ethoxycarbonylmethylamino)[3,5-dibromo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenoxy]methylphosphonamide

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[0730] The title compound was prepared from [3,5-dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)]phenoxy]methylphosphonic acid (compound 8-1) according to the procedures described for the synthesis of compound 15-17. MP 63-66 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.35 (s, 2H), 6.61 (m, 2H), 6.33 (m, 1H), 4.36 (d, *J* = 15.0 Hz, 2H), 4.15 (m, 4H), 3.80 (m, 4H), 3.20 (m, 1H), 2.17 (s, 6H), 1.28 (m, 6H), 1.15 (d, *J* = 7.0 Hz, 2H); LC-MS *m/z* = 667 [C<sub>24</sub>H<sub>31</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>8</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>24</sub>H<sub>31</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>8</sub>P + 0.1 CH<sub>3</sub>COCH<sub>3</sub>): C, 43.43; H, 4.74; N, 4.17. Found: C, 44.05; H, 4.47; N, 4.02; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = methanol-dichloromethane (1:24); R<sub>f</sub> = 0.22.

**Example 15-33:** Di-*N*-(*l*-1-ethoxycarbonyl-ethylamino)[3,5-dibromo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenoxy]methylphosphonamide

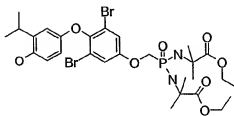


[0731] The title compound was prepared from [3,5-dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)]phenoxy]methylphosphonic acid (compound 8-1) according to the procedures described for the synthesis of compound 15-17. MP 62-65 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.35 (s, 2H), 6.61 (m, 2H), 6.33 (m, 1H), 4.36 (d, *J* = 15.0 Hz, 2H), 4.15 (m, 4H), 3.80 (m, 4H), 3.20 (m, 1H), 2.17 (s, 6H), 1.28 (m, 6H), 1.15 (d, *J* = 7.0 Hz, 2H); LC-MS *m/z* = 695 [C<sub>24</sub>H<sub>31</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>8</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>24</sub>H<sub>31</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>8</sub>P): C, 44.98; H, 5.08; N, 4.03. Found: C, 45.16; H, 5.07; N, 4.04; TLC conditions: Uniplat

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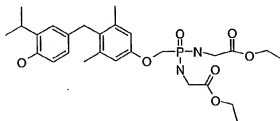
silica gel, 250 microns; Mobile phase = methanol-dichloromethane (1:24);  $R_f$  = 0.26.

**Example 15-34:** Di-*N*-(*l*-1-ethoxycarbonyl-1-methyl-ethylamino)[3,5-dibromo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenoxy]methylphosphonamide



[0732] The title compound was prepared from [3,5-dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)]phenoxy]methylphosphonic acid (compound 8-1) according to the procedures described for the synthesis of compound 15-1. MP 62-65 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.41 (s, 2H), 6.63 (m, 2H), 6.36 (m, 1H), 4.31 (d,  $J$  = 15.0 Hz, 2H), 4.15 (m, 5H), 3.20 (m, 1H), 1.61 (d,  $J$  = 25.0 Hz, 12H), 1.29 (m, 9H), 1.15 (d,  $J$  = 7.5 Hz, 6H); LC-MS  $m/z$  = 723 [ $\text{C}_{28}\text{H}_{39}\text{Br}_2\text{N}_2\text{O}_8\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{28}\text{H}_{39}\text{Br}_2\text{N}_2\text{O}_8\text{P}$ ): C, 46.55; H, 5.44; N, 3.88. Found: C, 46.71; H, 5.42; N, 3.90; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = methanol-dichloromethane (1:24);  $R_f$  = 0.41.

**Compound 15-35:** Di-*N*-(ethoxycarbonyl-methylamino)[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)phenoxy]methylphosphonamide

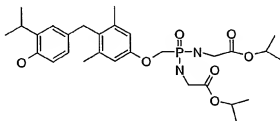


[0733] To a stirred solution of [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)]-phenoxy]methylphosphonic acid (example 7) (0.41 g, 1.11 mmol) and DMF (0.1 mL, 1.11 mmol) in dichloromethane (5:6 mL) at 0 °C was added oxalyl chloride (0.38 mL, 4.4 mmol). The reaction mixture was

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heated to 50 °C for 3 h, cooled to room temperature and concentrated under reduced pressure. To the residue at -78 °C was added a solution of glycine ethyl ester hydrochloride (0.65 g, 4.44 mmol) and triethylamine (1.25 mL, 8.88 mmol) in dichloromethane (5.3 mL). The reaction mixture was stirred for 14 h at room temperature, filtered to remove salts, and concentrated under reduced pressure. The residue was partitioned between ethyl acetate (50 mL) and aqueous NaHCO<sub>3</sub> solution (100 mL). The organic layer was separated, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>-MeOH (95:5) to afford the title compound as an off-white foam (41.3 mg, 20.2%). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.97 (s, 1H), 6.81 (s, 1H), 6.63 (s, 2H), 6.57 (d, *J* = 8.4 Hz, 1H), 6.43 (d, *J* = 7.8 Hz, 1H), 4.76 (m, 2H), 4.07 (m, 2H), 4.00 (d, *J* = 6.6 Hz, 2H), 3.78 (s, 1H), 3.66 (m, 4H), 3.08 (m, 1H), 2.15 (s, 6H), 1.16 (t, 6H), 1.07 (d, *J* = 6.6 Hz, 6H); LC-MS *m/z* = 535.3 [C<sub>27</sub>H<sub>39</sub>N<sub>2</sub>O<sub>7</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>27</sub>H<sub>39</sub>N<sub>2</sub>O<sub>7</sub>P): C, 60.66; H, 7.35; N, 5.24. Found: C, 60.51; H, 7.12; N, 4.93.

**Compound 15-36:** Di-*N*-(isopropoxyloxycarbonyl-methylamino)[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)phenoxyethyl]phosphonamide

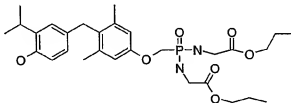


[0734] The title compound was prepared from [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)]-phenoxyethylphosphonic acid (example 7) and glycine *iso*-propylester hydrochloride according to the procedure described for the synthesis of compound 15-35. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.97 (s, 1H), 6.81 (s, 1H), 6.63 (s, 2H), 6.57 (d, *J* = 8.4 Hz, 1H), 6.43 (d, *J* = 7.8 Hz, 1H), 4.86 (m, 2H), 4.72 (m, 2H), 4.10 (d, *J* = 9.3 Hz, 2H), 3.78 (s, 2H), 3.61 (m, 4H), 3.12 (m, 1H), 2.14 (s, 6H), 1.14 (d, *J* = 6.0 Hz, 12H), 1.08 (d, *J* = 6.6

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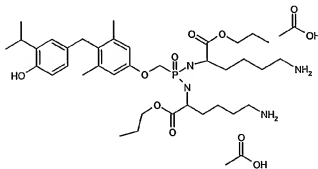
Hz, 6H); LC-MS  $m/z$  = 563.3 [ $C_{29}H_{43}N_2O_7P + H$ ]<sup>+</sup>; Anal. Calcd for ( $C_{29}H_{43}N_2O_7P$ ): C, 61.91; H, 7.70; N, 4.98. Found: C, 61.81; H, 7.69; N, 5.11.

**Compound 15-39:** Di-*N*-(propyloxycarbonyl-methylamino)[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)phenoxy]methyl]phosphonamide



[0735] The title compound was prepared from [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)]-phenoxyethylphosphonic acid (example 7) and glycine *n*-propylester hydrochloride according to the procedure described for the synthesis of compound 15-35: <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.96 (s, 1H), 6.81 (s, 1H), 6.62 (s, 2H), 6.57 (d, *J* = 8.4 Hz, 1H), 6.43 (d, *J* = 10.2 Hz, 1H), 4.78 (m, 2H), 4.08 (d, *J* = 9.0 Hz, 2H), 3.94 (t, 4H), 3.78 (s, 2H), 3.65 (m, 4H), 3.10 (m, 1H), 2.14 (s, 6H), 1.56 (m, 4H), 1.08 (d, *J* = 6.6 Hz, 6H), 0.87 (t, 6H); LC-MS  $m/z$  = 563.6 [ $C_{29}H_{43}N_2O_7P + H$ ]<sup>+</sup>; Anal. Calcd for ( $C_{29}H_{43}N_2O_7P + 0.1$  eq  $C_3H_6O$ ): C, 61.91; H, 7.73; N, 4.93. Found: C, 61.87; H, 8.12; N, 4.77.

**Compound 15-40:** Di-*N*-(*l*-1-propyloxycarbonyl-1-(5-pentylamino))[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propyl-benzyl)phenoxy]methyl]phosphonamide acetic acid salt

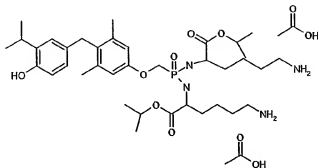


[0736] To a stirred suspension of 3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)phenoxyethylphosphonic acid (compound 7, 0.25 g, 0.68 mmol) in 1,2 dichloroethane (10 mL) at rt were added oxalylchloride (0.34 g,

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2.7 mmol) and DMF (0.1 mL, 0.68 mmol). The reaction mixture was heated at 50 °C for 3 h, and cooled to rt. The reaction mixture was concentrated under reduced pressure and azeotroped with toluene (2x10 mL). The crude compound was treated with lysine propylester (freebase form) (0.1.0 g, 2.72 mmol) and *N,N*-diisopropylethylamine (0.8 mL, 2.72 mmol) in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C. The reaction mixture was stirred for 14 h at rt and the reaction mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc (50 mL) and aqueous NaHCO<sub>3</sub> solution (50 mL). The organic layer was separated, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel, eluting with ethyl acetate:hexanes (3:2), treated with acetic acid and filtered to give the title compound as a white solid (78 mg, 92%, MP: 65-68 °C, 98% pure). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 6.81 (s, 1H), 6.69 (s, 2H), 6.61-6.55 (m, 2H), 4.25 (dd, *J* = 2.0, 6.4 Hz, 4H), 4.18-4.0 (m, 6H), 3.92 (s, 2H), 3.31-3.20 (m, 1H), 2.91 (q, *J* = 5.7 Hz, 4H), 2.24 (s, 2H), 1.93 (s, 3H), 1.80-1.50 (m, 14H), 1.14 (d, *J* = 6.6 Hz, 6H), 0.99 (t, *J* = 7.5 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H); LC-MS *m/z* = 705 [C<sub>37</sub>H<sub>61</sub>N<sub>4</sub>O<sub>7</sub>P+H]<sup>+</sup>; HPLC conditions: YMC packODS-Aq12S051546W column; mobile phase = CH<sub>3</sub>OH:5%TFA (7:3) flow rate = 1.0 mL/min; detection = UV 220, 254, 280 nm retention time in min: 13.20; Anal. Calcd: (MF:C<sub>37</sub>H<sub>61</sub>N<sub>4</sub>O<sub>7</sub>P + 2.0 AcOH + 1.5 H<sub>2</sub>O) Calcd: C:57.80, H:8.52, N:6.58; Found: C:57.53, H:8.67, N:6.25.

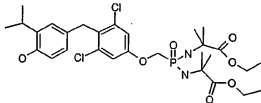
**Compound 15-41:** Di-*N*-(*l*-1-isopropoxyxycarbonyl-1-(5-pentylamino)) [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propyl-benzyl)phenoxy]methylphosphonamide acetic acid salt



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[0737] The title compound was prepared from 3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)phenoxyethyl]phosphonic acid (compound 7) according to the procedure described for the synthesis of compound 15-40 as a white solid: (100 mg, 95%, MP: 62-64 °C, 98% pure). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 6.82 (s, 1H), 6.70 (s, 2H), 6.62-6.56 (m, 2H), 4.25 (m, 2H), 4.05-4.0 (m, 2H), 3.92 (s, 2H), 3.30-3.20 (m, 1H), 2.98-2.38 (m, 4H), 2.24 (s, 2H), 2.02-1.40 (m, 16H), 1.30 (d, *J* = 6.6 Hz, 6H), 1.22 (d, *J* = 6.9 Hz, 6H), 1.14 (d, *J* = 6.9 Hz, 6H); LC-MS *m/z* = 705 [C<sub>37</sub>H<sub>61</sub>N<sub>4</sub>O<sub>7</sub>P+H]<sup>+</sup>; HPLC conditions: YMCpackSB-Aq12S051546W column; mobile phase = CH<sub>3</sub>OH:5%TFA (7:3) flow rate = 1.0 mL/min; detection = UV 220, 254, 280 nm retention time in min: 5.79; Anal. Calcd: (MF:C<sub>37</sub>H<sub>61</sub>N<sub>4</sub>O<sub>7</sub>P + 2.0 AcOH + 2.1 H<sub>2</sub>O) Calcd: C:57.07, H:8.55, N:6.49; Found: C:56.79, H:8.52, N:6.31.

**Compound 15-42:** Di-*N*-(1-ethoxycarbonyl-1-methylethylamino)[3,5-dichloro-4-(4'-hydroxy-3'-isopropylbenzyl)-phenoxyethyl]phosphonamide

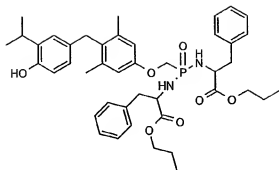


[0738] The title compound was prepared from [3,5-dichloro-4-(4'-hydroxy-3'-isopropylbenzyl)-phenoxyethyl]-phosphonic acid (example 7-5) according to the procedure described for the synthesis of example 15-1. MP 43-45 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.10 (s, 1H), 7.18 (s, 2H), 6.98 (s, 1H), 6.67 (m, 2H), 4.46 (d, *J* = 10.8 Hz, 2H), 4.06-4.63 (m, 9H), 3.14 (m, 1H), 1.43 (d, *J* = 11.4 Hz, 12H), 1.22 (t, 6H), 1.10 (d, *J* = 6.6 Hz, 6H); LC-MS *m/z* = 632 [C<sub>29</sub>H<sub>41</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>7</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>29</sub>H<sub>41</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>7</sub>P + 0.1 TFA): C, 54.55; H, 6.44; N, 4.36. Found: C, 54.44; H, 6.74; N, 4.48.

**Compound 15-43:** Di-*N*-(1-propyloxycarbonyl-2-phenylethylamino)[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonamide

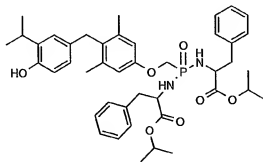


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[0739] The title compound was prepared from 3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)phenoxyethylphosphonic acid (compound 7) according to the procedure described for the synthesis of compound 15-1 to afford a white foam.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.99 (s, 1H), 7.30-7.13 (m, 10H), 6.83 (s, 1H), 6.62-6.45 (m, 3H), 4.73 (t,  $J = 11.7$  Hz, 1H), 4.36 (t,  $J = 11.7$  Hz, 1H), 4.06-3.80 (m, 6H), 3.80 (s, 2H), 3.63 (d,  $J = 9.3$  Hz, 2H), 3.17-3.08 (m, 1H), 2.95-2.75 (m, 4H), 2.17 (s, 6H), 1.55-1.42 (m, 4H), 1.09 (d,  $J = 6.9$  Hz, 6H), 0.85-0.74 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  18.87 (s); LC-MS  $m/z = 743$  [ $\text{C}_{43}\text{H}_{55}\text{N}_2\text{O}_7\text{P} + \text{H}$ ] $^+$ ; TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate/dichloromethane (2:1);  $R_f = 0.58$ ; Anal. Calcd for ( $\text{C}_{43}\text{H}_{55}\text{N}_2\text{O}_7\text{P} + 0.3 \text{ H}_2\text{O}$ ): C, 69.02; H, 7.49; N, 3.74. Found: C, 69.01, H, 7.60; N, 3.65.

**Compound 15-44:** Di-*N*-(1-isopropoxyxycarbonyl-2-phenylethylamino)-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)phenoxy]methylphosphonamide



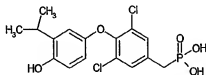
[0740] The title compound was prepared from 3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)phenoxyethylphosphonic acid (compound 7) according to

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the procedure described for the synthesis of compound 15-1 to afford a white foam.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.99 (s, 1H), 7.30-7.13 (m, 10H), 6.83 (s, 1H), 6.62-6.45 (m, 3H), 4.85-4.73 (m, 2H), 4.66 (t,  $J = 11.4$  Hz, 1H), 4.34 (t,  $J = 11.4$  Hz, 1H), 4.06-3.88 (m, 2H), 3.80 (s, 2H), 3.65 (d,  $J = 9.6$  Hz, 2H), 3.17-3.08 (m, 1H), 2.95-2.75 (m, 4H), 2.17 (s, 6H), 1.17-1.00 (m, 18H);  $^{31}\text{P}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  18.89 (s); LC-MS  $m/z = 743$  [ $\text{C}_{43}\text{H}_{55}\text{N}_2\text{O}_7\text{P} + \text{H}$ ] $^+$ ; TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate/dichloromethane (2:1);  $R_f = 0.56$ ; Anal. Calcd for ( $\text{C}_{43}\text{H}_{55}\text{N}_2\text{O}_7\text{P}$ ): C, 69.56; H, 7.46; N, 3.77. Found: C, 69.30, H, 7.59; N, 3.72.

### Example 16

**Compound 16:** 3,5-dichloro-4-(4'-hydroxy-3'-*iso*-propylphenoxy)benzylphosphonic acid



Step a:

[0741] To a solution of 3,5-dichloro-4-(4'-hydroxy-3'-*iso*-propylphenoxy)benzyl alcohol in  $\text{CH}_2\text{Cl}_2$  (5.0 mL) at  $-78^\circ\text{C}$  is added  $\text{BBr}_3$ . The reaction mixture is stirred at room temperature for 16 h, poured into ice water and extracted with ethyl acetate. The organic layer is dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product is purified by column chromatography on silica gel, eluting with acetone-hexanes to afford 3,5-dichloro-4-(4'-hydroxy-3'-*iso*-propylphenoxy)benzyl bromide.

Step b:

[0742] Diethyl 3,5-dichloro-4-(4'-hydroxy-3'-*iso*-propylphenoxy)benzyl phosphonate is prepared from 3,5-dichloro-4-(4'-hydroxy-3'-*iso*-

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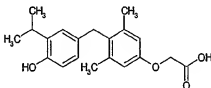
propylphenoxy)benzyl bromide by following the procedure described in example 9, step g.

Step c:

[0743] 3,5-Dichloro-4-(4'-hydroxy-3'-*iso*-propylphenoxy)benzylphosphonic acid is prepared from diethyl 3,5-dichloro-4-(4'-hydroxy-3'-*iso*-propylphenoxy)benzylphosphonate by following the procedure described in example 9, step h.

### Example 17

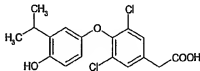
**Compound 17:** [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy] acetic acid



[0744] Compound 17 was synthesized by a literature method (G. Chiellini *et al. Bioorg. Med. Chem. Lett.* **2000**, *10*, 2607)

### Example 18

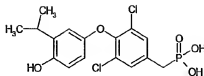
**Compound 18:** 3,5-dichloro-4-[4'-hydroxy-3'-*iso*-propylphenoxy] benzeneacetic acid



### Example 19

**Compound 19:** [3,5-dichloro-4-(4'-hydroxy-3'-*iso*-propylphenoxy)] benzylphosphonic acid

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Alternative synthesis for the compound of Example 16

Step a:

[0745] To a mixture of bis(4-methoxy-3-*iso*-propylphenyl)iodonium tetrafluoroborate (4.55 g, 8.88 mmol) and copper powder (0.88 g, 13.80 mmol) in  $\text{CH}_2\text{Cl}_2$  (40.0 mL) at 0 °C was added a solution of TEA (1.06 mL, 3.71 mmol) and methyl 3,5-dichloro-4-hydroxybenzoate (1.65 g, 6.90 mmol) in dichloromethane (20.0 mL). The reaction mixture was stirred at room temperature for 3 d and filtered through a Celite plug. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:19) to afford methyl 3,5-dichloro-4-(3'-*iso*-propyl-4'-methoxyphenoxy)benzoate as an orange oil (2.02 g, 80%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.10 (m, 1 H), 6.85 (m, 2 H), 6.50 (m, 1 H), 3.90 (s, 3 H), 3.76 (s, 3H), 3.21 (m, 1 H), 1.14 (d,  $J$  = 6.0 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-acetone (17:3);  $R_f$  = 0.51.

Step b:

[0746] To a mixture of methyl 3,5-dichloro-4-(3'-*iso*-propyl-4'-methoxyphenoxy)benzoate (1.40 g, 3.37 mmol) in THF (10.0 mL) at 0 °C was added a solution of DIBAL-H (8.12 mL, 8.12 mmol, 1.0 M solution in THF). The reaction mixture was stirred at room temperature for 16 h, quenched with cold 1 N HCl and diluted with ethyl acetate. The organic layer was washed with 1 N HCl and brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to afford 4-(3'-*iso*-propyl-4'-methoxyphenoxy)-3,5-dichlorobenzyl alcohol as an off-white solid (0.94 g, 100%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.54 (s, 2 H), 6.81 (m, 2 H), 6.40 (m, 1 H), 5.51 (m, 1 H), 4.54 (d,  $J$  = 6.0 Hz, 2 H), 3.75 (s, 3 H), 3.21 (m, 1 H),

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1.13 (d,  $J = 6.0$  Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-acetone (17:3);  $R_f = 0.27$ .

Step c:

[0747] To a stirred solution of triphenylphosphine (0.42 g, 1.61 mmol) and  $\text{CBr}_4$  (0.534 g, 1.61 mmol) in diethyl ether (15.0 mL) at room temperature was added 4-(3'-*iso*-propyl-4'-methoxyphenoxy)-3,5-dichlorobenzyl alcohol (0.50 g, 1.46 mmol). The reaction mixture was stirred at room temperature for 16 h, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:9) to afford 3,5-dichloro-4-(3'-*iso*-propyl-4'-methoxyphenoxy)benzylbromide (0.320 g, 54%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.77 (s, 2 H), 6.82 (m, 2 H), 6.38 (m, 1 H), 4.75 (s, 2 H), 3.75 (s, 3 H), 3.22 (m, 1 H), 1.13 (d,  $J = 6.0$  Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-acetone (1:4);  $R_f = 0.46$ .

Step d:

[0748] A mixture of 3,5-dichloro-4-(3'-*iso*-propyl-4'-methoxyphenoxy)benzyl bromide (0.61 g, 1.51 mmol) and triethylphosphite (0.61 g, 3.56 mmol) in DMF (2.0 mL) was heated under reflux for 4 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with water and brine. The organic layer was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with acetone-hexanes (3:7) to afford diethyl 3,5-dichloro-4-(3'-*iso*-propyl-4'-methoxyphenoxy)benzylphosphonate as an oil (0.59 g, 85%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.55 (s, 2 H), 6.88 (d,  $J = 9.0$  Hz, 1 H), 6.75 (d,  $J = 3.0$  Hz, 1 H), 6.43 (m, 1 H), 4.01 (m, 4 H), 3.75 (s, 3 H), 3.41 (m, 2 H), 3.22 (m, 1 H), 1.20 (m, 6 H), 1.12 (d,  $J = 6.0$  Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (4:1);  $R_f = 0.22$ .

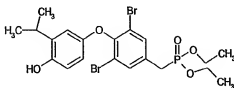
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Step e:

[0749] To a solution of diethyl 3,5-dichloro-4-(3'-*iso*-propyl-4'-methoxyphenoxy)benzylphosphonate (0.59 g, 1.28 mmol) in  $\text{CH}_2\text{Cl}_2$  (10.0 mL) at  $-30^\circ\text{C}$  was added bromotrimethylsilane (2.53 mL, 19.2 mmol). The reaction mixture was stirred at room temperature for 16 h and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (25.0 mL), cooled to  $-78^\circ\text{C}$  and to it was added  $\text{BBR}_3$  (19.0 mL, 19.0 mmol, 1.0 M solution in  $\text{CH}_2\text{Cl}_2$ ). The reaction mixture was stirred at  $-78^\circ\text{C}$  for 10 min, allowed to warm to room temperature and stirred for 16 h. The reaction mixture was poured into ice, concentrated and extracted with ethyl acetate. The organic layer was washed with water (20 mLx2), dried over  $\text{MgSO}_4$  and filtered. The solvent was removed under reduced pressure to afford 3,5-dichloro-4-(3'-*iso*-propyl-4'-hydroxyphenoxy)benzylphosphonic acid as a brown solid (0.20 g, 40%); mp:  $178\text{--}181^\circ\text{C}$ ; LC-MS  $m/z = 391$  [ $\text{C}_{16}\text{H}_{17}\text{Cl}_2\text{O}_3\text{P} - \text{H}^-$ ];  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.08 (s, 1 H), 7.48 (s, 2 H), 6.72 (m, 2 H), 6.25 (m, 1 H), 3.18 (m, 1 H), 3.00 (d,  $J = 21.0$  Hz, 2 H), 3.11 (m, 1 H), 1.14 (d,  $J = 6.0$  Hz, 6 H); Anal. Calcd for ( $\text{C}_{16}\text{H}_{17}\text{Cl}_2\text{O}_3\text{P} + 0.2 \text{ C}_4\text{H}_8\text{O}_2 + 0.5 \text{ H}_2\text{O}$ ): C, 48.30; H, 4.73. Found: C, 48.69, H, 5.16.

[0750] Using the appropriate starting material, compounds 19-1 to 19-3 was prepared in an analogous manner to that described for the synthesis of compound 19.

**Compound 19-1:** diethyl [3,5-dibromo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)] benzylphosphonate

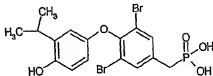


[0751] Prepared from methyl 3,5-dibromo-4-hydroxybenzoate (*J. Med. Chem.* 2003, 46, 1580) according to the procedure described for the synthesis of compound 19. mp:  $145^\circ\text{C}$ ; LC-MS  $m/z = 536$  [ $\text{C}_{20}\text{H}_{25}\text{Br}_2\text{O}_3\text{P} + \text{H}^+$ ];  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.53 (s, 2 H), 6.50 (m, 2 H), 6.23 (m, 1 H), 3.98 (m, 4

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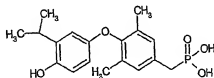
H), 3.11 (m, 1 H), 1.21 (m, 6 H), 1.02 (d,  $J = 6.0$  Hz, 6 H); Anal. Calcd for ( $C_{20}H_{25}Br_2O_3P$ ): C, 44.80; H, 4.70. Found: C, 45.19, H, 4.80.

**Compound 19-2:** [3,5-dibromo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)]benzylphosphonic Acid



[0752] Prepared from compound 19-1 according to the procedure described for the synthesis of compound 19 step e. mp: 76-79 °C; LC-MS  $m/z = 480$  [ $C_{16}H_{17}Br_2O_3P + H$ ] $^+$ ;  $^1H$  NMR (300 MHz,  $CD_3OD$ ):  $\delta$  7.52 (s, 2 H), 6.55 (m, 2 H), 6.20 (m, 1 H), 3.14 (m, 1 H), 3.00 (d,  $J = 21.0$  Hz, 2 H), 1.06 (d,  $J = 6.0$  Hz, 6 H); HPLC conditions: Column = 3 Chromolith SpeedRODs RP-18e, 100x4.6 mm; Mobile phase = Solvent A (Acetonitrile) = HPLC grade acetonitrile; Solvent B (buffer) = 20 mM ammonium phosphate buffer (pH 6.1, 0.018 M  $NH_4H_2PO_4$ /0.002 M  $(NH_4)_2HPO_4$ ) with 5% acetonitrile. Flow rate = 4 mL/min; UV@ 255 nm. Retention time in minutes. (rt = 5.80, 96% purity).

**Compound 19-3:** [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylphenoxy)]benzylphosphonic acid

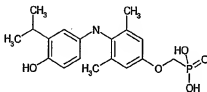


[0753] Prepared from methyl 3,5-dimethyl-4-hydroxybenzoate according to the procedure described for the synthesis of compound 19. mp: 79-82 °C; LC-MS  $m/z = 351$  [ $C_{18}H_{23}O_3P + H$ ] $^+$ ;  $^1H$  NMR (300 MHz,  $CD_3OD$ ):  $\delta$  6.93 (s, 2 H), 6.51 (m, 2 H), 6.13 (m, 1 H), 3.13 (m, 1 H), 2.98 (d,  $J = 21.0$  Hz, 2 H), 1.96 (s, 6 H), 1.04 (d,  $J = 6.0$  Hz, 6 H); Anal. Calcd for ( $C_{18}H_{23}O_3P + 1.2 H_2O$ ): C, 58.12; H, 6.88. Found: C, 58.01; H, 7.00.

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## Example 20

**Compound 20** [3,5-dimethyl-4-*N*-(4'-hydroxy-3-*iso*-propylphenylamino)phenoxy]methylphosphonic acid



Step a:

[0754] A solution of 4-amino-3,5-dimethylphenol (5.0 g, 36.46 mmol, Fieser, L. F. *Organic Syntheses*, Collect Vol II, 1943, 39), imidazole (6.21 g, 77.37 mmol) and triisopropylsilyl chloride (7.70 g, 40.1 mmol) in  $\text{CH}_2\text{Cl}_2$  (80 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (100.0 mL) and washed with water and brine. The organic layer was dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:19) to afford 2,6-dimethyl-4-triisopropylsilyloxyphenylamine (8.46 g, 79%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.57 (s, 2 H), 2.19 (s, 6 H), 1.23 (m, 3 H), 1.12 (m, 18 H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:9);  $R_f$  = 0.51.

Step b:

[0755] A mixture of  $\text{Pd}_2(\text{dba})_3$  (800 mg, 0.87 mmol) and BINAP (1.09 g, 1.75 mmol) in toluene (70 mL) at 100 °C in a sealed tube was heated for 30 min. The reaction mixture was cooled to room temperature and to it was added 2,6-dimethyl-4-triisopropylsilyloxyphenylamine (6.15 g, 20.98 mmol) followed by 4-bromo-2-*iso*-propyl-1-methoxymethoxybenzene (4.0 g, 17.48 mmol) and potassium *tert*-butoxide (2.18 g, 22.72 mmol). The reaction mixture was heated at 110 °C in the sealed tube for 16 h, cooled to room temperature and filtered through a plug of Celite. The solvent was removed under reduced



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pressure and the crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:9) to afford *N, N*-(2,6-dimethyl-4-triisopropylsilyloxyphenyl)-(3-*iso*-propyl-4-methoxymethoxyphenyl)amine as a yellow solid (4.8 g, 58%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.88 (d,  $J = 8.7$  Hz, 1 H), 6.67 (s, 1 H), 6.41 (d,  $J = 2.7$  Hz, 1 H), 6.22 (m, 1 H), 5.11 (s, 2 H), 3.52 (s, 3 H), 3.28 (m, 1 H), 2.17 (s, 6 H), 1.28 (m, 3 H), 1.15 (m, 24 H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:9);  $R_f = 0.70$ .

## Step c:

[0756] To a solution of *N, N*-(2,6-dimethyl-4-triisopropylsilyloxyphenyl)-(3-*iso*-propyl-4-methoxymethoxyphenyl)amine (800 mg, 1.70 mmol) in THF (10.0 mL) at 0 °C was added TBAF (2.55 mmol, 1.0 M in THF). The reaction mixture was stirred at room temperature for 16 h, diluted with ethyl acetate (10.0 mL) and quenched with  $\text{H}_2\text{O}$  (10.0 mL). The aqueous layer was extracted with ethyl acetate (10.0 mL) and the combined organic layers were dried over  $\text{MgSO}_4$ . The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:4) to afford 3,5-dimethyl-4-*N*-(3-*iso*-propyl-4'-methoxymethoxyphenylamino)phenol (280 mg, 52%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.88 (d,  $J = 8.1$  Hz, 1 H), 6.63 (s, 2 H), 6.47 (m, 1 H), 6.21 (m, 1 H), 5.12 (s, 2 H), 3.52 (s, 3H), 3.30 (m, 1 H), 2.19 (s, 6 H), 1.2 (d, 6 H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:9);  $R_f = 0.45$ .

## Step d:

[0757] To a solution of sodium hydride (22 mg, 0.86 mmol) in DMF at 0 °C was added a solution of 3,5-dimethyl-4-*N*-(3-*iso*-propyl-4'-methoxymethoxyphenylamino)phenol (270 mg, 0.86 mmol) in DMF (2.0 mL). The reaction mixture was stirred at room temperature for 1 h and to it was added a solution of diethyl tosyloxymethylphosphonate (0.34 g, 1.03 mmol) in DMF (1.0 mL). The reaction mixture was stirred at room temperature for 16 h

and the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate (10.0 mL) and saturated aqueous  $\text{NaHCO}_3$  (10.0 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (10.0 mL). The combined organic layers were dried over  $\text{MgSO}_4$ , filtrated and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:1) to afford diethyl [3,5-dimethyl-4-*N*-(3-*iso*-propyl-4'-methoxymethoxyphenylamino)phenoxy]methylphosphonate (160 mg, 52%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.88 (d,  $J$  = 8.4 Hz, 1 H), 6.75 (s, 2 H), 6.46 (m, 1 H), 6.20 (m, 1 H), 5.12 (s, 2 H), 4.25 (m, 6 H), 3.52 (s, 3 H), 3.28 (m, 1 H), 2.21 (s, 6 H), 1.40 (m, 6 H), 1.20 (d,  $J$  = 6.9 Hz, 6 H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:9);  $R_f$  = 0.29.

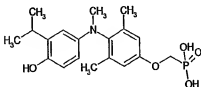
Step c:

[0758] To a solution of diethyl [3,5-dimethyl-4-*N*-(3-*iso*-propyl-4'-methoxymethoxyphenylamino)phenoxy]methylphosphonate (150 mg, 0.32 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at room temperature was added TMSBr (0.51 mL, 3.88 mmol). The reaction mixture was stirred at room temperature for 16 h and the solvent was removed under reduced pressure. The residue was treated with water (5.0 mL), stirred for 2 h and extracted with ethyl acetate (10.0 mLx2). The combined organic layers were dried over  $\text{MgSO}_4$ , filtrated and concentrated under reduced pressure. The crude product was purified by preparatory LC-MS to afford [3,5-dimethyl-4-*N*-(4'-hydroxy-3-*iso*-propylphenylamino)phenoxy]methylphosphonic acid as a blue solid (40 mg, 33.9%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.3 (s, 1 H), 6.74 (s, 2 H), 6.49 (d,  $J$  = 8.4 Hz, 1 H), 6.36 (d,  $J$  = 2.4 Hz, 1 H), 5.92 (m, 1 H), 4.05 (d,  $J$  = 10.5 Hz, 2 H), 3.11 (m, 1H), 2.10 (s, 6 H), 1.10 (d,  $J$  = 6.9 Hz, 6 H). mp > 200 °C; LC-MS  $m/z$  = 366  $[\text{C}_{18}\text{H}_{24}\text{NO}_5\text{P} + \text{H}]^+$ ; Anal. Calcd for  $(\text{C}_{18}\text{H}_{24}\text{NO}_5\text{P} + 0.5 \text{H}_2\text{O} + 0.2 \text{HCl})$ : C, 56.65; H, 6.66; N, 3.67. Found: C, 56.45; H, 6.73; N, 3.71.

[0759] Using the appropriate starting material, compound 20-1 was prepared in an analogous manner to that described for the synthesis of compound 20.

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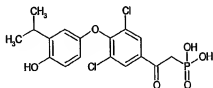
**Compound 20-1** [3,5-dimethyl-4-(4'-hydroxy-3-*iso*-propylphenyl methylamino)phenoxy]methylphosphonic acid



[0760] Prepared by standard reductive amination (*J. Org. Chem.* 1972, 37, 1673) of *N*, *N*-(2,6-dimethyl-4-triisopropylsilyloxyphenyl)-(3-*iso*-propyl-4-methoxymethoxyphenyl)amine with formaldehyde followed by the same procedure described for the synthesis compound 20. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.28 (s, 1 H), 6.76 (s, 2 H), 6.54 (d, *J* = 8.8 Hz, 1 H), 6.15 (m, 1 H), 5.94 (m, 1 H), 4.05 (d, *J* = 10.2 Hz, 2 H), 3.13 (m, 1 H), 3.02 (s, 3 H), 1.97 (s, 6 H), 1.06 (d, *J* = 7.0 Hz, 6 H). mp > 200 °C. LC-MS *m/z* = 379 [C<sub>19</sub>H<sub>26</sub>NO<sub>5</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>19</sub>H<sub>26</sub>NO<sub>5</sub>P + 0.3 HBr + 0.1 CH<sub>2</sub>Cl<sub>2</sub>): C, 55.41; H, 6.46; N, 3.38. Found: C, 55.35; H, 6.55; N, 3.43.

### Example 21

**Compound 21:** 2-[3,5-dichloro-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenyl]-2-oxoethylphosphonic acid



Step a:

[0761] To a stirred solution of diethyl methylphosphonate (0.4 g, 2.6 mmol) in anhydrous THF (15 mL) at -78 °C was added *n*-BuLi (1.95 mL, 1.95 mmol, 1 M solution in hexanes). The reaction mixture was stirred at -78 °C for 1 h and to it was added a solution of methyl 3,5-dichloro-4-(3'-*iso*-propyl-4'-methoxyphenoxy)benzoate (0.24 g, 0.65 mmol, step a, example 19) in THF (5 mL). The reaction mixture was stirred at -78 °C for 1 h, quenched with 10%

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AcOH (10 mL) and H<sub>2</sub>O (50 mL) and extracted with ethyl acetate (50 mLx2). The combined organic layers were washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:1) to afford diethyl 2-[3,5-dichloro-4-(3'-*iso*-propyl-4'-methoxyphenoxy)]-2-oxoethylphosphonate as a colorless oil (0.28 g, 63%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.05 (s, 2 H), 6.85 (d, *J* = 3.3 Hz, 1 H), 6.71 (d, *J* = 9.0 Hz, 1 H), 6.40 (dd, *J* = 3.3, 9.0 Hz, 1 H), 4.08 (q, *J* = 6.3 Hz, 1 H), 3.81 (s, 3 H), 3.60 (d, *J* = 23.1 Hz, 2 H), 3.35 - 3.25 (m, 1 H), 1.32 (t, *J* = 6.9 Hz, 6 H), 1.19 (d, *J* = 6.9 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (2:3); R<sub>f</sub> = 0.2.

Step b:

[0762] To a stirred solution of diethyl 2-[3,5-dichloro-4-(3'-*iso*-propyl-4'-methoxyphenoxy)]-2-oxoethylphosphonate (0.26 g, 0.54 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (7 mL) at 0 °C was added TMSBr (0.83 g, 0.8 mL, 5.4 mmol). The reaction mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature and stirred for 16 h. The solvent was removed under reduced pressure and the residue was dissolved in CH<sub>3</sub>OH (3 mL). The solvent was removed under reduced pressure to afford 2-[3,5-dichloro-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenyl]-2-oxoethylphosphonic acid as a white solid (0.2 g, 83%): <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 8.09 (s, 2 H), 6.83 (d, *J* = 3.3 Hz, 1 H), 6.71 (d, *J* = 9.0 Hz, 1 H), 6.40 (dd, *J* = 3.3, 9.0 Hz, 1 H), 3.81 (s, 3 H), 3.60 (d, *J* = 22.1 Hz, 2 H), 3.35-3.25 (m, 1 H), 1.19 (d, *J* = 6.9 Hz, 6 H).

Step c:

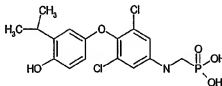
[0763] To a stirred solution of 2-[3,5-dichloro-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenyl]-2-oxoethylphosphonic acid (0.17 g, 0.40 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at -78 °C was added BBr<sub>3</sub> (1.0 mL, 1.0 mmol, 1.0 M in CH<sub>2</sub>Cl<sub>2</sub>). The reaction mixture was stirred at room temperature for 14 h, poured into ice water (25 mL) and stirred for 1 h. The reaction mixture was extracted with ethyl acetate (50 mLx2). The combined organic layers were

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washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was recrystallized from  $\text{CH}_2\text{Cl}_2$ , filtered and dried to afford 2-[3,5-dichloro-4-(4'-hydroxy-3'-*iso*-propylphenoxy) phenyl]-2-oxoethylphosphonic acid as a yellow solid (0.14 g, 92%, m.p.: 83-85 °C, 98% pure):  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  8.18 (s, 2 H), 6.71 (d,  $J = 3.0$  Hz, 1 H), 6.65 (d,  $J = 8.7$  Hz, 1 H) 6.37 (dd,  $J = 3.0, 8.7$  Hz, 1 H), 3.65 (d,  $J = 37.8$  Hz, 2 H) 3.30 - 3.20 (m, 1 H), 1.18 (d,  $J = 6.9$  Hz, 6 H); LC-MS  $m/z = 420$  [ $\text{C}_{17}\text{H}_{17}\text{Cl}_2\text{O}_6\text{P} + \text{H}$ ] $^+$ ; HPLC conditions: ODSAQ AQ-303-5 column; mobile phase =  $\text{CH}_3\text{OH}:\text{TFA}$  (7:3) flow rate = 1.0 mL/min; detection = UV @ 254 nm retention time in min: 13.26; Anal Calcd: ( $\text{C}_{17}\text{H}_{17}\text{Cl}_2\text{O}_6\text{P}$ ) Calcd: C: 48.09; H: 4.18. Found: C, 47.97; H: 4.39.

### Example 22

**Compound 22:** [3,5-dichloro-4-(4'-hydroxy-3'-*iso*-propylphenoxy) phenylamino]methylphosphonic acid



Step a:

[0764] To a solution of 4-amino-2,6-dichlorophenol (4.0 g, 22.5 mmol) in THF (25 mL) was added *t*-BOC anhydride (5.88 g, 27.0 mmol). The reaction mixture was heated under reflux for 2.5 h and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:9) to afford 3,5-dichloro-4-hydroxyphenylcarbamic acid *t*-butyl ester as an off-white solid (5.80 g, 93%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.70 (s, 1 H), 9.44 (s, 1 H), 7.46 (s, 2 H), 1.48 (s, 9 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = acetone-hexanes (3:7);  $R_f = 0.39$ .

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## Step b:

[0765] To a mixture of bis(4-methoxy-3-*iso*-propylphenyl)iodonium tetrafluoroborate (2.76 g, 5.39 mmol) and copper powder (0.46 g, 7.18 mmol) in  $\text{CH}_2\text{Cl}_2$  (20.0 mL) at 0 °C was added a solution of TEA (0.55 mL, 3.95 mmol) and 3,5-dichloro-4-hydroxyphenylcarbamic acid *tert*-butyl ester (1.00 g, 3.59 mmol) in dichloromethane (10.0 mL). The reaction mixture was stirred at room temperature for 14 h and filtered through a Celite plug. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:19) to afford 3,5-dichloro-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenylcarbamic acid *tert*-butyl ester as an off-white solid (1.45 g, 95%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.81 (s, 1 H), 7.68 (m, 2 H), 6.79 (m, 2 H), 6.42 (m, 1 H), 3.75 (s, 3 H), 3.20 (m, 1 H), 1.51 (s, 9 H), 1.33 (d,  $J = 6.0$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = acetone-hexanes (3:7);  $R_f = 0.64$ .

## Step c:

[0766] To a mixture of 3,5-dichloro-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenylcarbamic acid *tert*-butyl ester (0.400 g, 0.94 mmol) in THF (12.0 mL) at 0 °C was added sodium hydride (0.064 g, 1.22 mmol, 60% dispersion in oil). The reaction mixture was stirred at room temperature for 1 h and cooled to 0 °C. To the stirring mixture was added diethyl trifluoromethanesulfonyloxymethylphosphonate (0.18 g, 0.94 mmol). The reaction mixture was stirred at room temperature for 2 h, quenched with water and diluted with ethyl acetate. The organic layer was washed with water and brine and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (2:3) to afford diethyl *N*-*tert*-butoxycarbonyl-[3,5-dichloro-4-(3-*iso*-propyl-4'-methoxyphenoxy)phenylamino]methylphosphonate as an oil (0.34 g, 63%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.64 (s, 2 H), 6.90 (m, 1 H), 6.76 (s, 1 H), 6.45 (m, 1 H), 4.95 (d,  $J = 9.0$  Hz, 2 H), 4.01 (m, 4 H), 3.76 (s, 3 H), 3.21 (m, 1 H), 1.43 (s, 9 H), 1.20 (m, 6 H), 1.13 (d,  $J = 6.0$  Hz, 6 H); TLC

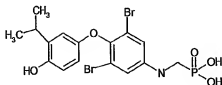
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conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (2:3);  $R_f = 0.15$

Step d:

[0767] To a solution of diethyl *N*-*tert*-butoxycarbonyl-[3,5-dichloro-4-(3-*iso*-propyl-4'-methoxy-phenoxy)phenylamino]methyl]phosphonate (0.25 g, 0.43 mmol) in  $\text{CH}_2\text{Cl}_2$  (6.0 mL) at 0 °C was added bromotrimethylsilane (0.86 mL, 6.50 mmol). The reaction mixture was stirred at room temperature 16 h and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (5.0 mL), cooled to -78 °C and to it was added  $\text{BBr}_3$  (2.84 mL, 2.84 mmol, 1.0 M solution in  $\text{CH}_2\text{Cl}_2$ ). The reaction mixture was stirred at -78 °C for 10 min, allowed to warm to room temperature and stirred for 16 h. The reaction mixture was poured into ice, diluted with ethyl acetate and washed with water. The organic layer was dried over  $\text{MgSO}_4$  and concentrated under reduced pressure to afford [3,5-dichloro-4-(4'-hydroxy-3-*iso*-propylphenoxy)phenylamino]methylphosphonic acid as an off-white solid (0.15 g, 85% over two steps): mp: 97-100 °C; LC-MS  $m/z = 405.407$  [ $\text{C}_{16}\text{H}_{18}\text{Cl}_2\text{NO}_5\text{P} + \text{H}^+$ ] $^+$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.02 (s, 2 H), 6.90 (m, 2 H), 6.71 (m, 2 H), 6.32 (m, 2 H), 3.36 (m, 2 H), 3.21 (m, 1 H), 1.17 (d,  $J = 6.0$  Hz, 6 H); Anal. Calcd for  $(\text{C}_{16}\text{H}_{18}\text{Cl}_2\text{NO}_5\text{P} + 0.1 \text{ C}_4\text{H}_8\text{O}_2 + 0.3 \text{ H}_2\text{O})$ : C, 46.85; H, 4.65; N, 3.33. Found: C, 47.09; H, 4.94; N, 3.50.

**Compound 22-1:** [3,5-dibromo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenylamino]methylphosphonic acid



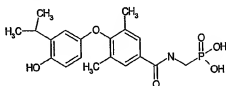
[0768] The title compound was prepared from 4-amino-2,6-dibromophenol according to the procedure described for the synthesis of Example 22, steps a-d;  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.95 (m, 1H), 7.02 (s, 2H), 6.63 (m, 2H), 6.23 (m, 1H), 3.31 (d,  $J = 12.0$  Hz, 2H), 3.14 (m, 1H), 1.12 (d,  $J = 6.0$  Hz, 6H); LC-MS  $m/z = 496$  [ $\text{C}_{16}\text{H}_{18}\text{Br}_2\text{NO}_5\text{P} + \text{H}^+$ ] $^+$ ; HPLC conditions: Column =

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Agilent zorbax RP18, 150×3.0 mm; Mobile phase = Solvent B (Acetonitrile) = HPLC grade acetonitrile; Solvent A (buffer) = 20 mM potassium phosphate buffer (pH 4.7). Flow rate = 0.75 mL/min; UV@ 254 nm. Retention time in minutes. (rt = 8.70/20 min, 92% purity).

### Example 23

**Compound 23:** *N*-[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylphenoxy)benzamido]methyl phosphonic acid



Step a:

[0769] To a solution of methyl 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)benzoate (8.53 g, 16.7 mmol, intermediate for the synthesis of Example 19-3) in methanol (60.0 mL) at 0 °C was added a solution of 1 N NaOH (28.15 mL, 28.15 mmol). The reaction mixture was stirred at room temperature for 16 h and acidified with cold concentrated HCl. The reaction mixture was extracted with ethyl acetate (10.0 mL) and the organic layer was dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure to afford 4-(3'-*iso*-propyl-4'-methoxyphenoxy)-3,5-dimethylbenzoic acid as a pink solid (1.38 g, 78%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 12.88 (s, 1 H), 7.76 (s, 2 H), 6.85 (m, 1 H), 6.75 (m, 1 H), 6.34 (m, 1 H), 3.73 (s, 3H), 3.20 (m, 1 H), 2.11 (s, 6 H), 1.12 (d, *J* = 6.0 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-acetone (17:3); R<sub>f</sub> = 0.00.

Step b:

[0770] To a mixture of 4-(3'-*iso*-propyl-4'-methoxyphenoxy)-3,5-dimethylbenzoic acid (0.20 g, 0.63 mmol), diethyl aminomethylphosphonate (0.19 g, 0.76 mmol) and triethylamine in CH<sub>2</sub>Cl<sub>2</sub> (10.0 mL) at 0 °C was added EDCI (0.18 g, 0.763 mmol) followed by 1-hydroxy-7-azabenzotriazole (0.09



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mg, 0.63 mmol). The reaction mixture was stirred at room temperature for 16 h, concentrated and diluted with ethyl acetate (10.0 mL). The organic layer was washed with water (10 mLx3) and brine, dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The crude product was purified by preparatory TLC to afford diethyl *N*-[3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)-benzamido]methylphosphonate as an oil (0.20 g, 68%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.77 (m, 1 H), 7.69 (s, 2 H), 6.84 (d,  $J$  = 9.0 Hz, 1 H), 6.75 (m, 1 H), 6.36 (m, 1 H), 4.05 (m, 4 H), 3.76 (m, 5 H), 3.21 (m, 1 H), 2.11 (s, 6 H), 1.21 (m, 6 H), 1.13 (d,  $J$  = 6.0 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-acetone (1:1);  $R_f$  = 0.28.

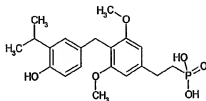
Step c:

[0771] To a solution of diethyl *N*-[4-(3'-*iso*-propyl-4'-methoxyphenoxy)-3,5-dimethylbenzamido]methyl]phosphonate (0.20 g, 0.43 mmol) in  $\text{CH}_2\text{Cl}_2$  (4.3 mL) at -30 °C was added bromotrimethylsilane (0.56 mL, 4.31 mmol). The reaction mixture was stirred at room temperature for 16 h and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (5.0 mL), cooled to -78 °C, and to it was added  $\text{BBr}_3$  (1.29 mL, 1.29 mmol, 1.0 M solution in  $\text{CH}_2\text{Cl}_2$ ). The reaction mixture was stirred at -78 °C for 3 h, allowed to warm to room temperature and stirred for 16 h. The reaction mixture was poured into ice, extracted with ethyl acetate (10.0 mL) and washed with 2% HCl (20 mLx2) and water (20 mLx2). The organic layer was dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to afford *N*-[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylphenoxy)benzamido]methylphosphonic acid as a pink solid (0.08 g, 47% over two steps): mp: 163-166 °C; LC-MS  $m/z$  = 394 [ $\text{C}_{19}\text{H}_{24}\text{NO}_6\text{P} + \text{H}$ ] $^+$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.52 (s, 2 H), 6.51 (m, 2 H), 6.19 (m, 1 H), 3.70 (d,  $J$  = 12.0 Hz, 2 H), 3.14 (m, 1 H), 2.04 (s, 6 H), 1.01 (d,  $J$  = 6.0 Hz, 6 H); Anal. Calcd for ( $\text{C}_{19}\text{H}_{24}\text{NO}_6\text{P} + 1.0 \text{ H}_2\text{O}$ ): C, 55.47; H, 6.37; N, 3.40. Found: C, 55.30; H, 6.32; N, 3.12.

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## Example 24

**Compound 24:** 2-[3,5-dimethoxy-4-(4'-hydroxy-3'-iso propylbenzyl)phenyl]ethylphosphonic acid



## Step a:

[0772] To a solution of 3,5-dimethoxy-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)phenol (0.6 g, 1.73 mmol, intermediate for the synthesis of Example 7-2) and DMAP (0.85 g, 6.92 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at 0 °C was slowly added trifluoromethanesulfonyl anhydride (0.44 mL, 2.6 mmol). The reaction mixture was stirred at 0 °C for 2 h and quenched by water (10.0 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:9) to afford 3,5-dimethoxy-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)-1-trifluoromethanesulfonyloxyphenyl as a light yellow oil (0.83 g, 100%); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.09 (s, 1 H), 6.87 (s, 2 H), 6.80 (s, 2 H), 5.15 (s, 2 H), 3.84 (s, 6 H), 3.81 (s, 2 H), 3.36 (s, 3 H), 3.20 (m, 1 H), 1.14 (d, *J* = 6.6 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:9); R<sub>f</sub> = 0.73.

## Step b:

[0773] A mixture of 3,5-dimethoxy-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)-1-trifluoromethanesulfonyloxyphenyl (0.83 g, 1.73 mmol), triethylamine (0.96 mL, 6.92 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (0.12 g, 0.17 mmol) and diethyl vinylphosphonate (0.37 mL, 2.43 mmol) in DMF (8 mL) was heated at 80 °C for 16 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and saturated aqueous

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NaHCO<sub>3</sub>. The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-CH<sub>2</sub>Cl<sub>2</sub> (1:1) to afford diethyl 2-[4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)-3,5-dimethoxyphenyl]vinylphosphonate as a light yellow oil (0.1 g, 12%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.50 (d, *J* = 17.4 Hz, 1 H), 7.29 (s, 1 H), 7.11 (m, 2 H), 6.72 (s, 2 H), 6.22 (t, *J* = 17.1 Hz, 1 H), 5.17 (s, 2 H), 4.21 (m, 4 H), 3.96 (s, 2 H), 3.87 (s, 6 H), 3.49 (s, 3 H), 3.31 (m, 1 H), 1.40 (t, *J* = 6.9 Hz, 6 H), 1.23 (d, *J* = 6.6 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-CH<sub>2</sub>Cl<sub>2</sub> (1:3); R<sub>f</sub> = 0.4.

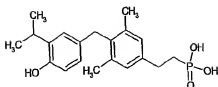
Step c:

[0774] A mixture of diethyl 2-[3,5-dimethoxy-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)phenyl]vinylphosphonate (0.1 g, 0.2 mmol) and Pd/C (20 mg, 10%) in MeOH (20 mL) was stirred under one atmosphere of hydrogen at room temperature for 16 h. The mixture was filtered through a Celite plug. The solvent was removed under reduced pressure and the residue (90 mg) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL). Deprotection with TMSBr as described for the synthesis of Compound 7, step b afforded 2-[3,5-dimethoxy-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenyl]ethylphosphonic acid as light pink foam (73 mg, 91%). <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 8.88 (s, 1 H), 7.01 (d, *J* = 1.8 Hz, 1 H), 6.71 (dd, *J* = 1.8 Hz, *J* = 8.0 Hz, 1 H), 6.55 (d, *J* = 8.4 Hz, 1 H), 6.5 (s, 2 H), 3.76 (s, 6 H), 3.69 (s, 2 H), 3.08 (m, 1 H), 2.72 (m, 2 H), 1.82 (m, 2 H), 1.08 (d, *J* = 7.0 Hz, 6 H), LC-MS *m/z* = 395 [C<sub>20</sub>H<sub>27</sub>O<sub>6</sub>P + H]<sup>+</sup>; Anal Calcd for (C<sub>20</sub>H<sub>27</sub>O<sub>6</sub>P + 1.3 H<sub>2</sub>O): C, 57.49; H, 7.14. Found: C, 57.24; H, 7.24.

[0775] Using the appropriate starting material, compounds 24-1 to 24-4 were prepared in an analogous manner to that described for the synthesis of compound 24.

**Compound 24-1:** 2-[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenyl]ethylphosphonic acid

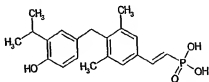
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[0776] Prepared from 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)phenol (Chiellini *et al.*, *Bioorg. Med. Chem. Lett.* 10:2607 (2000)).

mp: 65-68 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 6.93 (s, 2 H), 6.86 (d, *J* = 1.8 Hz, 1 H), 6.60 (d, *J* = 8.4 Hz, 1 H), 6.54 (dd, *J* = 1.8 Hz, *J* = 8.0 Hz, 1 H), 3.94 (s, 2 H), 3.24 (m, 1 H), 2.82 (m, 2 H), 2.23 (s, 6 H), 2.01 (m, 2 H), 1.15 (d, *J* = 7.0 Hz, 6 H), LC-MS *m/z* = 363 [C<sub>20</sub>H<sub>27</sub>O<sub>4</sub>P]<sup>+</sup>; Anal Calcd for (C<sub>20</sub>H<sub>27</sub>O<sub>4</sub>P + 0.6 H<sub>2</sub>O + 0.4 CH<sub>3</sub>OH): C, 63.47; H, 7.78. Found: C, 63.39; H, 8.06.

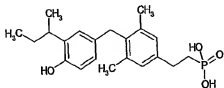
**Compound 24-2:** *trans*-2-[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenyl]vinylphosphonic acid



[0777] Prepared from 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)phenol (Chiellini *et al.*, *Bioorg. Med. Chem. Lett.* 10:2607 (2000)).

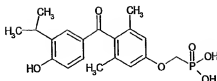
mp: 82-84 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.38 (m, 1 H), 7.27 (s, 2 H), 6.84 (d, *J* = 1.8 Hz, 1 H), 6.62 (d, *J* = 8.4 Hz, 1 H), 6.54 (dd, *J* = 1.8 Hz, *J* = 8.0 Hz, 1 H), 6.42 (m, 1 H), 4.00 (s, 2 H), 3.24 (m, 1 H), 2.28 (s, 6 H), 1.15 (d, *J* = 7.0 Hz, 6 H), LC-MS *m/z* = 361 [C<sub>20</sub>H<sub>25</sub>O<sub>4</sub>P + H]<sup>+</sup>; Anal Calcd for (C<sub>20</sub>H<sub>25</sub>O<sub>4</sub>P + 0.3 H<sub>2</sub>O): C, 65.67; H, 7.05. Found: C, 65.43; H, 7.13.

**Compound 24-3:** 2-[4-(3'-*sec*-butyl-4'-hydroxy-benzyl)-3,5-dimethylphenyl]-ethylphosphonic acid





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## Step a:

- [0780] To a stirring solution of (2,6-dimethyl-4-trisopropylsilyloxyphenyl)-(3'-*iso*-propyl-4'-methoxymethoxyphenyl)methanol (0.620 g, 1.27 mmol), (Chiellini *et al.*, *Bioorg. Med. Chem. Lett.* 10:2607 (2000)) in THF (10.0 mL) at 0 °C was added tetrabutylammonium fluoride (1.91 mL, 1.91 mmol, 1.0 M solution in THF). The reaction mixture was stirred at room temperature for 20 min, diluted with diethyl ether and washed with water (20 mLx2) and brine. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:4) to afford 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzylhydroxy)phenol as an oil (0.370 g, 88%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.07 (s, 1 H), 7.20 (m, 1 H), 6.90 (m, 1 H), 6.78 (m, 1 H), 6.39 (s, 2 H), 5.98 (d, *J* = 3.0 Hz, 1 H), 5.52 (d, *J* = 3.0 Hz, 1 H), 5.18 (s, 2H), 3.38 (s, 3 H), 3.25 (m, 1 H), 2.12 (s, 6 H), 1.16 (m, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (4:1); R<sub>f</sub> = 0.15.

## Step b:

- [0781] To a mixture of 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzylhydroxy)phenol (0.380 g, 1.15 mmol) in DMF (10.0 mL) at 0 °C was added Cs<sub>2</sub>CO<sub>3</sub> (1.87 g, 5.75 mmol). After 5 min, diethyl trifluoromethanesulfonyloxymethyl phosphonate (0.24 g, 1.15 mmol) was added. The reaction mixture was stirred at 0 °C for 5 h, allowed to warm to room temperature and stirred for 16 h. The reaction mixture was quenched with 1 N HCl, diluted with ethyl acetate, and washed with water (10 mLx4) and brine. The organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:4) as mobile phase to afford diethyl [3,5-dimethyl-4-(3'-

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*iso*-propyl-4'-methoxymethoxybenzylhydroxy)phenoxy]methylphosphonate as an oil (0.41 g, 74%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.20 (m, 1 H), 6.92 (m, 1 H), 6.78 (m, 1 H), 6.67 (s, 2 H), 6.03 (d, *J* = 3.0 Hz, 1 H), 5.64 (d, *J* = 3.0 Hz, 1 H), 5.18 (s, 2H), 4.38 (d, *J* = 9.0 Hz, 2 H), 4.11 (m, 4 H), 3.38 (s, 3 H), 3.25 (m, 1 H), 2.19 (s, 6 H), 1.24 (m, 6 H), 1.16 (m, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-acetone (6:4); R<sub>f</sub> = 0.35.

Step c:

[0782] To a stirred solution of diethyl [3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzylhydroxy)phenoxy]methylphosphonate (0.32 g, 0.66 mmol) in dichloromethane (8.0 mL) at 0 °C was added Dess-Martin periodinane (2.08 mL, 0.99 mmol, 0.48 M solution in CH<sub>2</sub>Cl<sub>2</sub>). The reaction mixture was stirred room temperature for 16 h, concentrated, diluted with diethyl ether (10.0 mL). To the solution was added a solution of 580 mg of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> pentahydrate in 60 mL saturated NaHCO<sub>3</sub>. After 15 min, the reaction mixture was diluted with ethyl acetate and water and washed with saturated NaHCO<sub>3</sub> and brine. The organic layer was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:1) to afford diethyl [3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzoyl)phenoxy]methylphosphonate as an oil (0.285 g, 89%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.22 (m, 1 H), 7.43 (m, 1 H), 7.13 (m, 1 H), 6.85 (s, 2 H), 5.35 (s, 2H), 4.49 (d, *J* = 7.5 Hz, 2 H), 4.16 (m, 4 H), 3.43 (s, 3 H), 3.27 (m, 1 H), 2.02 (s, 6 H), 1.29 (m, 6 H), 1.20 (m, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = dichloromethane-methanol (3:97); R<sub>f</sub> = 0.52.

Step d:

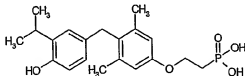
[0783] To a solution of diethyl [3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzoyl)phenoxy]methylphosphonate (0.075 g, 0.16 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) at -30 °C was added bromotrimethylsilane (0.31 mL, 2.4 mmol). The reaction mixture was stirred at room temperature 16 h and the

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solvent was removed under reduced pressure. The residue was treated with acetonitrile-water (4:1, 5.0 mL) and sonicated. The solvents were removed under reduced pressure. The residue was dissolved in 1 N NaOH and extracted with dichloromethane and ethyl acetate. The aqueous layer was acidified with 2 N HCl and extracted with ethyl acetate. The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to afford [3,5-dimethyl-4-(4'-hydroxy-3-*iso*-propylbenzoyl)phenoxy]methylphosphonic acid as a pink solid (0.05 g, 84%): mp 138 °C; LC-MS *m/z* = 379 [C<sub>19</sub>H<sub>23</sub>O<sub>6</sub>P + H]<sup>+</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 10.50 (s, 1 H), 7.64 (s, 1 H), 7.27 (m, 1 H), 6.87 (m, 1 H), 6.78 (m, 1 H), 4.18 (m, 2 H), 3.18 (m, 1 H), 2.00 (s, 6 H), 3.11 (m, 1 H), 1.17 (d, *J* = 6.0 Hz, 6 H); HPLC conditions: Column = 3 Chromolith SpeedRODs RP-18e, 100×4.6 mm; Mobile phase = Solvent A (Acetonitrile) = HPLC grade acetonitrile; Solvent B (buffer) = 20 mM ammonium phosphate buffer (pH 6.1, 0.018 M NH<sub>4</sub>H<sub>2</sub>PO<sub>4</sub>/0.002 M (NH<sub>4</sub>)<sub>2</sub>HPO<sub>4</sub>) with 5% acetonitrile. Flow rate = 4 mL/min; UV@ 255 nm. Retention time in minutes. (rt = 5.30, 95% purity).

### Example 26

**Compound 26:** 2-[3,5-dimethyl-4-(3'-*iso*-propyl-4'-hydroxybenzyl)phenoxy]ethylphosphonic acid



Step a:

[0784] To a stirring solution of 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxymethylbenzyl)phenol (1.00 g, 3.18 mmol, Chiellini *et al.*, *Bioorg. Med. Chem. Lett.* 10:2607 (2000)) in DMF (30.0 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (5.18 g, 15.90 mmol) followed by 1,2-dibromoethane (1.64 g, 19.08 mmol). The reaction mixture was stirred at 60 °C for 2 d, diluted with ethyl acetate and washed with water (20 mLx4) and brine. The organic layer was



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dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:19) to afford 1-(2-bromoethoxy)-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)-3,5-dimethylbenzene as an oil (0.26 g, 16%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.94 (m, 2 H), 6.67 (m, 3 H), 5.18 (s, 2 H), 4.32 (m, 2 H), 3.95 (s, 2 H), 3.68 (m, 2 H), 3.51 (s, 3 H), 3.37 (s, 3 H), 3.32 (m, 1 H), 2.26 (s, 6 H), 1.22 (d,  $J = 6.0$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (4:1);  $R_f = 0.91$ .

## Step b:

[0785] A mixture of 1-(2-bromoethoxy)-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)-3,5-dimethylbenzene (0.15 g, 0.36 mmol) and triethylphosphite (0.18 g, 1.07 mmol) in DMF (2.0 mL) was heated under reflux for 4 h. The reaction mixture was cooled to rt, diluted with ethyl acetate and extracted with water (10 mLx4) and brine. The organic layer was dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:1) to afford diethyl 2-[3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)phenoxy]ethylphosphonate as an oil (0.085 g, 50%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  6.96 (m, 1 H), 6.89 (m, 1 H), 6.62 (m, 3 H), 5.16 (s, 2 H), 4.12 (m, 2 H), 4.07 (m, 4 H) 3.86 (s, 2 H), 3.37 (s, 3 H), 3.22 (m, 1 H), 2.30 (m, 2 H), 2.17 (s, 6 H), 1.25 (m, 6 H), 1.12 (d,  $J = 6.0$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (3:7);  $R_f = 0.10$ .

## Step c:

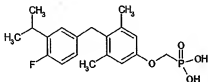
[0786] Deprotection of diethyl 2-[3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)phenoxy]ethylphosphonate with bromotrimethylsilane afforded 2-[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]ethylphosphonic acid as a brown oil (0.055 g, 87%): mp: 58-61 °C; LC-MS  $m/z = 379$ ,  $[\text{C}_{20}\text{H}_{27}\text{O}_5\text{P} + \text{H}]^+$ ;  $^1\text{H}$  NMR (300 MHz,

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CD<sub>3</sub>OD):  $\delta$  6.84 (s, 1 H), 6.66 (s, 2 H), 6.56 (m, 2 H), 4.26 (m, 2 H), 3.90 (s, 2 H), 3.22 (m, 1 H), 2.30 (m, 1 H), 2.22 (s, 6 H), 1.15 (d,  $J = 6.0$  Hz, 6 H); Anal. Calcd for (C<sub>20</sub>H<sub>27</sub>O<sub>5</sub>P + 0.6 H<sub>2</sub>O): C, 61.72; H, 7.30. Found: C, 61.96; H, 7.73.

### Example 27

**Compound 27:** [3,5-dimethyl-4-(4'-fluoro-3'-*iso*-propylbenzyl)phenoxy]methylphosphonic acid



Step a:

[0787] To a solution of 2-bromopropene (6.0 g, 49.60 mmol) in diethyl ether (200 mL) at -78 °C was added *t*-butyllithium (36.0 mL). The reaction mixture was stirred at -78 °C for 3 h and to it was added tributyltin chloride (16.1 g, 49.60 mmol). The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The reaction mixture was filtered through a plug of Celite and the filtrate was washed with saturated NH<sub>4</sub>Cl. The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated to afford the crude product as colorless oil that was used for next step without further purification.

Step b:

[0788] To a solution of 3-bromo-4-fluorobenzaldehyde (1.23 g, 6.04mmol) in dioxane (20 mL) was added the product obtained from *step a* followed by Pd(Ph<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>. The reaction mixture was heated at 110 °C for 16 h, cooled to room temperature and filtered through a plug of Celite. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:19) to afford 4-fluoro-3-isopropenylbenzaldehyde (500 mg, 50%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.89 (m, 1 H), 7.82 (m, 1 H), 7.24(m, 1 H), 5.36 (s, 2

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H), 2.21 (s, 3 H). TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:19);  $R_f$  = 0.60.

Step c:

[0789] To a solution of 4-bromo-3,5-dimethyl-triisopropylsilanoxybenzene (1.29 g, 3.6 mmol, Chiellini *et al.*, *Bioorg. Med. Chem. Lett.* 10:2607 (2000)) in THF at -78 °C was added *n*-butyllithium (1.58 mL, 3.96 mmol, 2.5 M in THF). After 30 min, a solution of 4-fluoro-3-isopropenylbenzaldehyde (500 mg, 3.0 mmol) in THF was added. The reaction mixture was stirred at -78 °C for 1 h, allowed to warm to room temperature, diluted with EtOAc and quenched with water. The organic layer was dried over  $MgSO_4$ , filtered and concentrated to afford crude 1-(2,6-dimethyl-4-triisopropylsilanyloxyphenyl)-1-(4'-fluoro-3'-isopropenylphenyl)methanol as an oil:  $^1H$  NMR (200 MHz,  $CDCl_3$ ):  $\delta$  7.18 (m, 1 H), 7.02 (m, 1 H), 6.94 (m, 1 H), 6.56 (s, 2 H), 6.22 (s, 1 H), 5.18 (m, 2 H), 2.20 (s, 6 H), 2.08 (s, 3 H), 1.25 (m, 3 H), 1.11 (m, 18).

Step d:

[0790] A solution of 1-(2,6-dimethyl-4-triisopropylsilanyloxyphenyl)-1-(4'-fluoro-3'-isopropenylphenyl)methanol (1.2 g, 2.71 mmol) and Pd/C (0.1 g, 10%) in EtOH/HOAc (9:1, 10 mL) was stirred under a  $H_2$  atmosphere for 16 h. The reaction mixture was filtrated through a plug of Celite and concentrated to afford the crude 3,5-dimethyl-4-(4'-fluoro-3'-isopropylbenzyl)triisopropylsilanoxybenzene that was used for the next step without further purification.

Step e:

[0791] To a solution of 3,5-dimethyl-4-(4'-fluoro-3'-isopropylbenzyl)triisopropylsilanoxybenzene in THF (10 mL) at 0 °C was added TBAF (1 M, 4.0 mL). The reaction mixture was stirred for 3 h, diluted with ethyl acetate 920 mL and quenched with water (10 mL). The organic layer was dried over  $MgSO_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting

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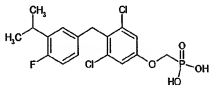
with ethyl acetate-hexanes (1:9) to afford 3,5-dimethyl-4-(4'-fluoro-3'-*iso*-propylbenzyl)phenol (450 mg, 61% for two steps):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.97 (d,  $J = 7.4$  Hz, 1 H), 6.86 (m, 1 H), 6.69 (m, 1 H), 6.60 (s, 2 H), 3.95 (s, 2 H), 3.20 (m, 1 H), 2.22 (s, 6 H), 1.25 (d,  $J = 6.4$  Hz, 6 H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:9);  $R_f = 0.50$ .

Step f:

[0792] [3,5-Dimethyl-4-(4'-fluoro-3'-*iso*-propylbenzyl)phenoxy]methyl phosphonic acid was prepared from 3,5-dimethyl-4-(4'-fluoro-3'-*iso*-propylbenzyl)phenol following the same procedure as described in compound 7, step b:  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.03 (m, 1 H), 6.93 (m, 1 H), 6.71 (s, 2 H), 6.64 (m, 1 H), 4.03 (d,  $J = 10.2$  Hz, 2 H), 3.89 (s, 2 H), 3.09 (m, 1 H), 2.15 (s, 6 H), 1.16 (d,  $J = 6.6$  Hz, 6 H). mp:  $> 200$  °C; LC-MS  $m/z = 367$  [ $\text{C}_{19}\text{H}_{24}\text{FO}_4\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{19}\text{H}_{24}\text{FO}_4\text{P} + 0.4 \text{ H}_2\text{O}$ ): C, 61.09; H, 6.69. Found: C, 60.85; H, 6.32.

[0793] Using the appropriate starting material, compound 27-1 was prepared in an analogous manner to that described for the synthesis of compound 27.

**Compound 27-1:** [3,5-dichloro-4-(4'-fluoro-3'-*iso*-propyl-benzyl)-phenoxy]methylphosphonic acid



[0794] Intermediate (2,6-dichloro-4-triisopropylsilyloxy-phenyl)-(4-fluoro-3-*iso*-propyl-phenyl)-methanol was prepared by the procedure described for the synthesis of compound 27, steps a, b, c, d as an oil (520 mg, 98%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.24 (m, 1H), 6.98 (m, 2H), 6.91 (s, 2H), 6.52 (s, 1H), 4.48 (s, 1H), 3.24 (m, 1H), 1.25 (m, 3H), 1.15 (s, 24H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:19);  $R_f = 0.86$ .

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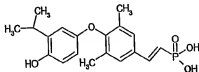
Step d:

[0795] To a solution of (2,6-dimethyl-4-triisopropylsilyloxy-phenyl)-(4-fluoro-3-*iso*-propyl-phenyl)-methanol (520 mg, 1.08 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added TFA (1.53 M, 0.7 mL) followed by triethylsilane (0.6 mL, 3.77 mmol) at r.t. After stirring for 2h, the reaction mixture was diluted with EtOAc and water and the layers were separated. The aqueous layer was further extracted with EtOAc. The combined organic layers were washed with Sat.  $\text{NaHCO}_3$ , water and brine, dried over  $\text{MgSO}_4$ , filtered and concentrated. The residue was purified by column chromatography (silica gel, hexanes) to provide 3,5-dichloro-4-(4'-fluoro-3'-*iso*-propyl-benzyl)-phenoxy]-triisopropylsilane as a colorless liquid (360 mg, 72%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.11 (m, 1H), 6.91 (m, 4H), 4.21 (s, 2H), 3.19 (m, 1H), 1.24 (m, 3H), 1.17 (m, 24H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes;  $R_f$  = 0.68.

[0796] Intermediate 3,5-dichloro-4-(4'-fluoro-3'-*iso*-propyl-benzyl)-phenoxy]-triisopropylsilane was transformed into the title compound by the procedure described for the synthesis of compound 35, steps e, f and h to give a white solid (55 mg, 35%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.22 (s, 2H), 7.18 (m, 1H), 7.04 (m, 1H), 6.87 (m, 1H), 4.22 (d,  $J$  = 9.6 Hz, 2H), 6.60 (s, 2H), 3.12 (m, 1H), 1.19 (d,  $J$  = 6.9 Hz, 6H). mp = 132~135, LC-MS  $m/z$  = 408  $[\text{C}_{17}\text{H}_{18}\text{Cl}_2\text{FO}_4\text{P} + \text{H}]^+$ ; Anal. Calcd for  $(\text{C}_{17}\text{H}_{18}\text{Cl}_2\text{FO}_4\text{P} + 0.2 \text{ H}_2\text{O})$ : C, 49.70; H, 4.51. Found: C, 49.58; H, 4.24.

### Example 28

**Compound 28:** *trans*-2-[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenyl]vinylphosphonic acid



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## Step a:

[0797] To a mixture of bis(4-methoxy-3-*iso*-propylphenyl)iodonium tetrafluoroborate (4.80 g, 9.38 mmol) and copper powder (0.79 g, 12.52 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15.0 mL) at 0 °C was added a solution of triethylamine (0.96 mL, 6.89 mmol) and 3,5-dimethyl-4-hydroxybenzaldehyde (0.94 g, 6.26 mmol) in dichloromethane (15.0 mL). The reaction mixture was stirred at room temperature for 3 d and filtered through a Celite plug. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:19) to afford 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)benzaldehyde as an oil (2.00 g, 100%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.96 (s, 1 H), 7.75 (s, 2 H), 6.85 (m, 1 H), 6.73 (m, 1 H), 6.36 (m, 1 H), 3.74 (s, 3 H), 3.19 (m, 1 H), 2.15 (s, 6 H), 1.12 (d, *J* = 6.0 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-acetone (17:3); R<sub>f</sub> = 0.51.

## Step b:

[0798] To a mixture of tetraethyl methylenediphosphonate (0.20 mL, 0.80 mmol) and THF (7.0 mL) at 0 °C was added sodium hydride (0.033 g, 0.804 mmol, 60% dispersion in oil). The reaction mixture was stirred at room temperature for 30 min and to it was added 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)benzaldehyde (0.20 g, 0.67 mmol). The reaction mixture was stirred at room temperature for 1 h, quenched with cold aqueous solution of NH<sub>4</sub>Cl, diluted with ethyl acetate and washed with water and brine. The solvent was removed under reduced pressure and the residue was purified by preparatory TLC on silica gel, eluting with acetone-hexanes (1:4) to afford diethyl *trans*-2-[3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenyl]vinylphosphonate as an oil (0.21 g, 74%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.53 (s, 2 H), 7.32 (m, 2 H), 6.84 (m, 1 H), 6.74 (m, 1 H), 6.59 (m, 2 H), 6.36 (m, 1 H), 4.00 (m, 4 H), 3.73 (s, 3 H), 3.20 (m, 1 H), 2.07 (s, 6 H), 1.27 (m, 6 H), 1.10 (d, *J* = 6.0 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-acetone (4:1); R<sub>f</sub> = 0.13.

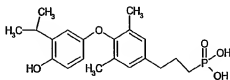
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Step c:

[0799] To a solution of diethyl *trans*-2-[3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenyl]vinylphosphonate (0.22 g, 0.50 mmol) in  $\text{CH}_2\text{Cl}_2$  (5.0 mL) at  $-30\text{ }^\circ\text{C}$  was added bromotrimethylsilane (0.66 mL, 5.00 mmol). The reaction mixture was stirred at room temperature 16 h and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (5.0 mL) and cooled to  $-78\text{ }^\circ\text{C}$ . To it was added  $\text{BBr}_3$  (1.49 mL, 1.49 mmol, 1.0 M solution in  $\text{CH}_2\text{Cl}_2$ ). The reaction mixture was stirred at  $-78\text{ }^\circ\text{C}$  for 3 h, allowed to warm to room temperature and stirred for 16 h. The reaction mixture was poured into ice, concentrated, and extracted with ethyl acetate. The organic solution was washed with 2% HCl (20 mL) and water (20 mLx3), dried over  $\text{MgSO}_4$  and filtered. The solvent was removed under reduced pressure to afford *trans*-2-[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenyl]vinylphosphonic acid as an off-white solid (0.08 g, 44% over two steps): mp  $92\text{--}94\text{ }^\circ\text{C}$ ; LC-MS  $m/z = 363$  [ $\text{C}_{19}\text{H}_{23}\text{O}_5\text{P} + \text{H}$ ] $^+$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.35 (s, 2 H), 7.10 (s, 1 H), 6.65 (s, 2 H), 6.32 (m, 2 H), 3.21 (m, 1 H), 2.12 (s, 6 H), 1.15 (d,  $J = 6.0\text{ Hz}$ , 6 H); HPLC conditions: Column = 3 Chromolith SpeedRODs RP-18e,  $100 \times 4.6\text{ mm}$ ; Mobile phase = Solvent A (Acetonitrile) = HPLC grade acetonitrile; Solvent B (buffer) = 20 mM ammonium phosphate buffer (pH 6.1, 0.018 M  $\text{NH}_4\text{H}_2\text{PO}_4/0.002\text{ M } (\text{NH}_4)_2\text{HPO}_4$ ) with 5% acetonitrile. Flow rate = 4 mL/min; UV@ 255 nm. Retention time in minutes. (rt = 5.71, 98% purity).

### Example 29

**Compound 29:** 3-[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenyl]propylphosphonic acid



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Step a:

[0800] To a mixture of triethyl phosphonoacetate (0.16 mL, 0.80 mmol) in THF (7.0 mL) at 0 °C was added NaH (0.033 g, 0.804 mmol, 60% dispersion in oil). The reaction mixture was stirred room temperature for 30 min and to it was added 3,5-dimethyl-4-(3-*iso*-propyl-4-methoxyphenoxy)benzaldehyde (0.20 g, 0.67 mmol, Example 28, step a). The reaction mixture was stirred at room temperature for 1 h, quenched with cold saturated NH<sub>4</sub>Cl, diluted with ethyl acetate and washed with water and brine. The solvent was removed under reduced pressure and the residue was purified by preparatory TLC on silica gel, eluting with acetone-hexanes (3:17) to afford ethyl *trans*-3-[3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenyl]acrylate as an oil (0.24 g, 97%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.60 (m, 3 H), 6.83 (m, 1 H), 6.76 (m, 1 H), 6.60 (m, 1 H), 6.36 (m, 1 H), 4.21 (m, 4 H), 3.73 (s, 3H), 3.21 (m, 1 H), 2.08 (s, 6 H), 1.27 (m, 6 H), 1.12 (d, *J* = 6.0 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-acetone (4:1); R<sub>f</sub> = 0.62.

Step b:

[0801] To a mixture of ethyl *trans*-3-[3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenyl]acrylate (1.10 g, 3.35 mmol) in THF (20.0 mL) at 0 °C was added DIBAL-H (4.68 mL, 4.68 mmol, 1.0 M solution in THF). The reaction mixture was stirred at room temperature for 2 h, quenched with cold 1 N HCl, diluted with ethyl acetate and washed with water and brine. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:9) to afford *trans*-3-[3,5-dimethyl 4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenyl]-prop-2-en-1-ol as an oil (0.50 g, 81%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.22 (s, 2 H), 6.97 (m, 0.5 H), 6.84 (m, 1.5 H), 6.73 (m, 1 H), 6.36 (m, 2 H), 4.87 (m, 1 H), 4.14 (m, 2 H), 3.73 (s, 3 H), 3.21 (m, 1 H), 2.05 (s, 6 H), 1.11 (d, *J* = 6.0 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-acetone (17:3); R<sub>f</sub> = 0.11.



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Step c:

[0802] To a mixture of *trans*-3-[3,5-dimethyl 4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenyl]-prop-2-en-1-ol (0.50 g, 1.53 mmol) in methanol (15.0 mL) was added 10% Pd/C (0.10 g, 20% wt/wt). The reaction mixture was stirred under H<sub>2</sub> (balloon) at room temperature for 6 h and filtered through a plug of Celite. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with acetone-hexanes (3:7) to afford 3-[3,5-dimethyl 4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenyl]propanol as an oil (0.36 g, 72%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 6.97 (s, 2 H), 6.82 (m, 1 H), 6.74 (m, 1 H), 6.30 (m, 1 H), 4.49 (m, 1 H), 3.73 (s, 3 H), 3.43 (m, 2 H), 3.21 (m, 1 H), 2.57 (m, 2 H), 2.03 (s, 6 H), 1.73 (m, 2 H), 1.11 (d, *J* = 6.0 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-acetone (17:3); R<sub>f</sub> = 0.26.

Step d:

[0803] To a stirred solution of triphenylphosphine (0.36 g, 1.39 mmol) and CBr<sub>4</sub> (0.46 g, 1.39 mmol) in diethyl ether (12.0 mL) at room temperature was added 3-[3,5-dimethyl 4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenyl]propanol (0.35 g, 1.06 mmol). The reaction mixture was stirred for 16 h, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:9) to afford 1-bromo-3-[3,5-dimethyl 4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenyl]propane as an oil (0.30 g, 72%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.00 (s, 2 H), 6.83 (m, 1 H), 6.80 (m, 1H), 6.31 (m, 1 H), 3.73 (s, 3 H), 3.53 (m, 2 H), 3.20 (m, 1 H), 2.70 (m, 2 H), 2.12 (m, 2 H), 2.03 (s, 6 H), 1.11 (d, *J* = 6.0 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-acetone (4:1); R<sub>f</sub> = 0.75.

Step e:

[0804] A mixture of 1-bromo-3-[3,5-dimethyl 4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenyl]propane (0.30 g, 0.77 mmol) and triethylphosphite (0.39 g, 2.31 mmol) in DMF (7.0 mL) was heated under reflux for 2.5 h and

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cooled to room temperature. The mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:3) to afford diethyl 3-[3,5-dimethyl 4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenyl]propylphosphonate as an oil (0.11 g, 32%):  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  6.97 (s, 2 H), 6.83 (d,  $J$  = 9.0 Hz, 1 H), 6.72 (d,  $J$  = 3.0 Hz, 1 H), 6.32 (m, 1 H), 3.99 (m, 4 H), 3.73 (s, 3 H), 3.35 (m, 2 H), 3.17 (m, 1 H), 2.62 (m, 2 H), 2.02 (s, 6 H), 1.75 (m, 4 H), 1.23 (m, 6 H), 1.10 (d,  $J$  = 6.0 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = acetone-hexanes (1:4);  $R_f$  = 0.17.

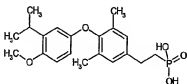
Step f:

[0805] To a solution of diethyl 3-[3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenyl]propylphosphonate (0.10 g, 0.22 mmol) in  $\text{CH}_2\text{Cl}_2$  (5.0 mL) at -30 °C was added bromotrimethylsilane (0.30 mL, 2.23 mmol). The reaction mixture was stirred at room temperature 16 h and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (3.0 mL) and cooled to -78 °C. To it was added  $\text{BBr}_3$  (0.66 mL, 0.66 mmol, 1.0 M solution in  $\text{CH}_2\text{Cl}_2$ ). The reaction mixture was stirred at -78 °C for 3 h, allowed to warm to room temperature and stirred for 16 h. The reaction mixture was poured into ice, concentrated and extracted with ethyl acetate (10 mL). The organic solution was washed with 0.5 M HCl (20 mLx2) and water (20 mLx2), dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to afford 3-[3,5-dimethyl 4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenyl]propylphosphonic acid as a white solid (0.50 g, 60% over two steps): mp: 60-63 °C; LC-MS  $m/z$  = 379 [ $\text{C}_{20}\text{H}_{27}\text{O}_5\text{P} + \text{H}^+$ ];  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  8.80 (s, 1 H), 6.85 (s, 2 H), 6.56 (m, 2 H), 6.10 (m, 1 H), 3.05 (m, 1 H), 2.40 (m, 2 H), 1.90 (s, 6 H), 1.49 (m, 2 H), 1.33 (s, 2 H), 1.03 (d,  $J$  = 6.0 Hz, 6 H); Anal. Calcd for ( $\text{C}_{20}\text{H}_{27}\text{O}_5\text{P} + 1.1 \text{ H}_2\text{O}$ ): C, 60.32; H, 7.39. Found: C, 60.19 H, 7.32.

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## Example 30

**Compound 30:** 2-[3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenyl]ethylphosphonic acid



Step a:

[0806] A solution of diethyl *trans*-2-[3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenyl]vinylphosphonate (1.77g, 4.10 mmol, Example 28, step b) and Pd/C (177mg) in EtOH/HOAc (10 mL, 9:1) was stirred under a H<sub>2</sub> atmosphere for 5 h. The reaction mixture was filtrated through a plug of Celite and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:1) to afford diethyl 2-[3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenyl]ethylphosphonate (1.29 g, 74%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 6.94 (s, 2 H), 6.81 (d, *J* = 3.0 Hz, 1 H), 6.68 (d, *J* = 8.7 Hz, 1 H), 6.36 (m, 1 H), 4.15 (m, 4 H), 3.30 (m, 1 H), 2.88 (m, 2 H), 2.13 (s, 6 H), 2.05 (m, 2 H), 1.37 (m, 6 H), 1.21 (d, *J* = 6.9 Hz, 6 H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:9); R<sub>F</sub> = 0.35.

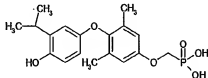
Step b:

[0807] Deprotection of diethyl 2-[3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenyl]ethylphosphonate with bromotrimethylsilane afforded 2-[3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenyl]ethylphosphonic acid: <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 6.98 (s, 2 H), 6.78 (d, *J* = 9.3 Hz, 1 H), 6.72 (d, *J* = 2.7 Hz, 1 H), 6.26 (m, 1 H), 3.70 (s, 3 H), 3.16 (m, 1 H), 2.71 (m, 2 H), 2.00 (s, 6 H), 1.81 (m, 2 H), 1.10 (d, *J* = 6.6 Hz, 6 H). LC-MS *m/z* = 379 [C<sub>20</sub>H<sub>27</sub>O<sub>5</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>20</sub>H<sub>27</sub>O<sub>5</sub>P + 0.7 H<sub>2</sub>O): C, 61.43; H, 7.32. Found: C, 61.59; H, 7.60.

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## Example 31

**Compound 31:** [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenoxy]methylphosphonic acid



[0808] To a solution of 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)benzaldehyde (0.18 g, 0.60 mmol, Example 28, step a) in dichloromethane (6.0 mL) at 0 °C was added *m*-chloroperoxybenzoic acid (0.22 g, 0.905 mmol). The reaction mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue was diluted with ethyl acetate. The organic solution was washed with saturated sodium bicarbonate (2x10mL) and water. The solvent was removed under reduced pressure and the residue was dissolved in methanol (5 mL). To the solution was added 1 N NaOH (1.81 mL, 1.81 mmol) and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with ethyl acetate, acidified with 2 N HCl and washed with brine. The solvent was evaporated and the residue was purified by preparatory TLC eluting with acetone-hexanes (1:4) to afford 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenol as an oil (0.08 g, 47%): <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 9.17 (s, 1 H), 6.82 (m, 1 H), 6.70 (m, 1 H), 6.51 (s, 2 H), 6.32 (m, 1 H), 3.71 (s, 3 H), 3.18 (m, 1 H), 1.95 (s, 6 H), 1.12 (d, *J* = 6.0 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-acetone (4:1); R<sub>f</sub> = 0.44.

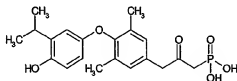
[0809] Intermediate 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenol was converted to [3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenoxy]methylphosphonic acid following the procedure described for the synthesis of compound 8: mp 60-64 °C; LC-MS *m/z* = 367 [C<sub>18</sub>H<sub>23</sub>O<sub>6</sub>P + H]<sup>+</sup>; <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 8.88 (s, 1 H), 6.76 (s, 2 H), 6.60 (m, 2 H), 6.17 (m, 1 H), 4.04 (d, *J* = 15.0 Hz, 2 H), 3.13 (m, 1 H),

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2.01 (s, 6 H), 1.10 (d,  $J = 6.0$  Hz, 6 H); Anal. Calcd for ( $C_{18}H_{23}O_6P + 0.7 H_2O$ ): C, 57.05; H, 6.49. Found: C, 57.10 H, 6.63.

### Example 32:

**Compound 32:** 3-[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylphenoxy)]phenyl-2-oxopropylphosphonic acid



Step a:

[0810] To a stirred solution of 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy) benzaldehyde (4.1 g, 15.2 mmol, Example 28, step a) in methanol (35 mL) at 0 °C was slowly added  $NaBH_4$  (1.16 g, 30.5 mmol). The reaction mixture was stirred at room temperature for 5 h and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (150 mL), washed with brine, dried over  $Na_2SO_4$  and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (2:4) to afford 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)benzyl alcohol as a white solid (3.4 g, 83%, m.p.: 78-80 °C):  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  7.12 (s, 2 H), 6.80 (d,  $J = 3.3$  Hz, 2 H), 6.67 (d,  $J = 9.0$  Hz, 1 H), 6.36 (dd,  $J = 3.0, 8.7$  Hz, 1 H), 4.68 (s, 2 H), 3.80 (s, 3 H), 3.35 - 3.25 (m, 1 H), 2.16 (s, 6 H), 1.19 (d,  $J = 7.2$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (2:4);  $R_f = 0.5$ .

Step b:

[0811] To a stirred solution of 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)benzyl alcohol (1.0 g, 3.4 mmol) in DME (10 mL) at 0 °C was added phosphorous tribromide (1.8 g, 0.5 mL, 6.8 mmol). The reaction mixture was stirred at 0 °C for 5 h, quenched with methanol (2 mL) and stirred

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for 30 min. The reaction mixture was poured into ice water and extracted with ether (100 mL). The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to afford crude 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)benzyl bromide as an oil (1.02 g, 82%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.15 (s, 2 H), 6.81 (d,  $J = 3.0$  Hz, 1 H), 6.67 (d,  $J = 9.0$  Hz, 1 H), 6.34 (dd,  $J = 3.0, 8.7$  Hz, 1 H), 4.51 (s, 2 H), 3.80 (s, 3 H), 3.40 - 3.25 (m, 1 H), 2.15 (s, 6 H), 1.20 (d,  $J = 7.2$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (2:4);  $R_f = 0.7$ .

## Step c:

[0812] To a stirred solution of sodium cyanide (0.23 g, 4.69 mmol) in  $\text{H}_2\text{O}$  (2 mL) at room temperature was added a solution of 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)benzyl bromide (0.85 g, 2.34 mmol) in ethanol (5 mL). The reaction mixture was heated at 80 °C for 2 h, cooled to room temperature, and poured into ice water (100 mL). The mixture was stirred for 1 h and extracted with ethyl acetate (2x100 mL). The combined organic layers were washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:4) to afford 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenylacetonitrile as a brown solid (0.64 g, 85%, m.p.: 56 - 58 °C):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.07 (s, 2 H), 6.78 (d,  $J = 3.3$  Hz, 1 H), 6.68 (d,  $J = 9.0$  Hz, 1 H), 6.35 (dd,  $J = 3.0, 8.7$  Hz, 1 H), 3.80 (s, 3 H), 3.73 (s, 2 H), 3.40 - 3.25 (m, 1 H), 2.16 (s, 6 H), 1.19 (d,  $J = 7.2$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (1:4);  $R_f = 0.5$ .

## Step d:

[0813] To a stirred solution of 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenylacetonitrile (0.75 g, 2.42 mmol) in acetic acid (7 mL) was added a 50% solution of  $\text{H}_2\text{SO}_4$  (14 mL). The reaction mixture was

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heated at 105 °C, for 3 h, cooled to room temperature and poured into ice water (100 mL). The mixture was stirred for 1 h and extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenylacetic acid as a brownish solid (0.62 g, 85%, m.p.: 118-120 °C): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.11 (s, 2 H), 6.82 (d, *J* = 2.7 Hz, 1 H), 6.80 (d, *J* = 8.7 Hz, 1 H), 6.37 (dd, *J* = 3.3, 8.7 Hz, 1 H), 3.80 (s, 3 H), 3.61 (s, 2 H), 3.38-3.25 (m, 1 H), 2.11 (s, 6 H), 1.17 (d, *J* = 7.2 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (1:1); R<sub>f</sub> = 0.2.

## Step e:

- [0814] To a stirred cold solution of methanol (15 mL) and acetyl chloride (3 mL, 86.0 mmol) at 0 °C was added dropwise a solution of 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenylacetic acid (0.7 g, 4.3 mmol) in methanol (5 mL). The reaction mixture was heated under reflux for 5 h and cooled to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (100 mL). The organic solution was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was triturated with hexane, filtered and dried under reduced pressure to afford methyl 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenylacetate as a yellow solid (0.69 g, 95%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.02 (s, 2 H), 6.82 (d, *J* = 2.7 Hz, 1 H), 6.66 (d, *J* = 8.7 Hz, 1 H), 6.38 (dd, *J* = 3.3, 8.7 Hz, 1 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 3.60 (s, 2 H), 3.28 - 3.25 (m, 1 H), 2.14 (s, 6 H), 1.20 (d, *J* = 7.2 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (1:1); R<sub>f</sub> = 0.6.

## Step f:

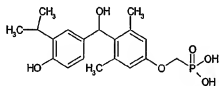
- [0815] 3-[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenyl]-2-oxopropylphosphonic acid was prepared from methyl-3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenoxy)phenylacetate following the same procedure as

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described in compound 21: mp: 80-82 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.85 (s, 2 H), 6.51 (d,  $J = 2.1$  Hz, 1 H), 6.48 (d,  $J = 8.4$  Hz, 1 H), 6.14 (dd,  $J = 3.0$ , 9.0 Hz, 1 H), 4.80 (s, 2 H), 3.80 (s, 2 H), 3.20-3.10 (m, 1 H), 2.99 (d,  $J = 22.5$  Hz, 1 H), 1.97 (s, 6 H), 1.03 (d,  $J = 6.9$  Hz, 6 H); LC-MS  $m/z = 393$  [ $\text{C}_{20}\text{H}_{25}\text{O}_6\text{P} + \text{H}$ ] $^+$ ; HPLC conditions: ODSAQ AQ-303-5 column; mobile phase =  $\text{CH}_3\text{OH}$ :5%TFA(7:3) flow rate = 1.0 mL/min; detection = UV @ 254 nm retention time in min: 11.19; Anal Calcd for ( $\text{C}_{20}\text{H}_{25}\text{O}_6\text{P} + 0.2 \text{CH}_2\text{Cl}_2$ ): C, 58.82; H, 6.22. Found: C, 58.75; H, 6.30.

### Example 33:

**Compound 33:** [3,5-dimethyl-4-(4'-Hydroxy-3'-*iso*-propyl-phenyl)methoxymethyl]phenoxy]methylphosphonic acid



#### Step a:

[0816] To a solution of (2,6-dimethyl-4-triisopropylsilyloxyphenyl)-(3-*iso*-propyl-4-methoxymethoxyphenyl)methanol (1.60 g, 3.29 mmol, Chiellini *et al.*, *Bioorg. Med. Chem. Lett.* 10:2607 (2000)) in THF (30.0 mL) at 0 °C was added TBAF (4.93 mL, 4.93 mmol, 1.0 M solution in THF). The reaction mixture was stirred at room temperature for 60 min, diluted with diethyl ether (10.0 mL) and washed with water (20 mLx2). The organic layer was dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:4) to afford 3,5-dimethyl-4-[(3'-*iso*-propyl-4'-methoxymethoxyphenyl)-hydroxymethyl]phenol as a white solid (1.00 g, 92%);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.05 (s, 1 H), 7.17 (m, 1 H), 6.90 (m, 1 H), 6.77 (m, 1 H), 6.37 (s, 2 H), 5.97 (d,  $J = 6.0$  Hz, 1 H), 5.51 (d,  $J = 6.0$  Hz, 1 H), 5.15 (s, 2 H), 3.36 (s, 3 H), 3.23 (m, 1 H), 2.10 (s, 6 H), 1.16 (m,



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6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (4:1);  $R_f$  = 0.17.

Step b:

[0817] To a mixture of 3,5-dimethyl-4-[(3'-*iso*-propyl-4'-methoxymethoxyphenyl)-hydroxymethyl]phenol (0.380 g, 1.15 mmol) in DMF (10.0 mL) at 0 °C was added  $\text{Cs}_2\text{CO}_3$  (1.87 g, 5.75 mmol). After 5 min, trifluoromethanesulfonic acid diethoxyphosphorylmethyl ester (0.24 g, 1.15 mmol) was added. The reaction mixture was stirred at room temperature for 16 h, quenched with 1 N HCl, diluted with ethyl acetate and extracted with water (10 mLx4). The organic layer was dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:4) to afford diethyl [3,5-dimethyl-4-[(3'-*iso*-propyl-4'-methoxymethoxyphenyl)-hydroxymethyl]phenoxy]methylphosphonate as an oil (0.41 g, 74%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.20 (m, 1 H), 6.92 (m, 1 H), 6.78 (m, 1 H), 6.67 (s, 2 H), 6.03 (d,  $J$  = 3.0 Hz, 1 H), 5.64 (d,  $J$  = 3.0 Hz, 1 H), 5.18 (s, 2H), 4.38 (d,  $J$  = 9.0 Hz, 2 H), 4.11 (m, 4 H), 3.38 (s, 3 H), 3.25 (m, 1 H), 2.19 (s, 6 H), 1.24 (m, 6 H), 1.16 (m, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-acetone (6:4);  $R_f$  = 0.35.

Step c:

[0818] To a solution of diethyl [3,5-dimethyl-4-[(3'-*iso*-propyl-4'-methoxymethoxyphenyl)-hydroxymethyl]phenoxy]methylphosphonate (0.200 g, 0.42 mmol) in MeOH (6.0 mL) at 0 °C was added 2 M HCl (2.1 mL, 4.20 mmol). The reaction mixture was stirred at 0 °C for 3 h and at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate (10.0 mL) and washed with water (20 mLx2). The organic layer was dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:1) to afford diethyl [3,5-dimethyl-4-[(4'-hydroxy-3'-*iso*-propylphenyl)methoxymethyl]phenoxy]methylphosphonate as an oil (0.125 g,

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69%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.16 (s, 1 H), 7.03 (s, 1 H), 6.71 (s, 2 H), 6.59 (m, 2 H), 5.63 (s, 2 H), 4.41 (d,  $J = 15.0$  Hz, 2 H), 4.11 (m, 4 H) 3.20 (s, 3H), 2.17 (s, 6 H), 1.21 (m, 6 H), 1.11 (m, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-acetone (1:1);  $R_f = 0.50$ .

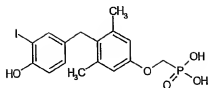
Step d:

[0819] To a solution of diethyl [3,5-dimethyl-4-[(4'-hydroxy-3'-*iso*-propylphenyl)methoxymethyl]phenoxy]methylphosphonate (0.065 g, 0.15 mmol) and 1,1,1,3,3,3- hexamethyldisilazane (0.38 mL, 1.80 mmol) in  $\text{CH}_2\text{Cl}_2$  (3.0 mL) at  $-30^\circ\text{C}$  was added bromotrimethylsilane (0.12 mL, 0.90 mmol). The reaction mixture was stirred at room temperature 16 h and the solvent was removed under reduced pressure. The residue was treated with acetonitrile-water (4:1, 5.0 mLx3) and sonicated. The solvent was removed under reduced pressure and the residue was dissolved in 1 M NaOH (5 mL). The aqueous solution was extracted with ethyl acetate (5mLx2) and acidified with 2 M HCl. The mixture was diluted with ethyl acetate and washed several times with water. The organic layer was dried over  $\text{MgSO}_4$  and concentrated under reduced pressure to afford the title compound as a red powder (0.035 g, 62%):  $^1\text{H}$  NMR (300 MHz,  $\text{D}_2\text{O}$ ):  $\delta$  7.03 (s, 1 H), 6.78-6.67 (m, 4 H), 6.14 (s, 1 H), 4.02 (d,  $J = 10.5$  Hz, 2 H), 3.21 (s, 3 H), 2.09 (s, 6 H), 1.01 (m, 6 H); HPLC conditions: Column = 3 Chromolith SpeedRODs RP-18e,  $100 \times 4.6$  mm; Mobile phase = Solvent A (Acetonitrile) = HPLC grade acetonitrile; Solvent B (buffer) = 20 mM ammonium phosphate buffer (pH 6.1, 0.018 M  $\text{NH}_4\text{H}_2\text{PO}_4$ /0.002 M  $(\text{NH}_4)_2\text{HPO}_4$ ) with 5% acetonitrile. Flow rate = 4 mL/min; UV@ 255 nm. Retention time in minutes. (rt = 5.70, 93% purity).

#### Example 34:

**Compound 34:** [3,5-dimethyl-4-(4'-hydroxy-3'-iodobenzyl)phenoxy] methylphosphonic acid

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## Step a

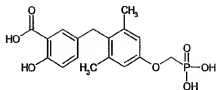
[0820] To a mixture of diethyl [3,5-dimethyl-4-(4'-methoxymethoxybenzyl)phenoxy]methylphosphonate (0.26 g, 0.61 mmol, prepared from commercially available 4-bromophenol according to the procedure described in compound 7) in methanol (3.0 mL) at 0 °C was added 2 N HCl (1.0 mL). The reaction mixture was stirred at room temperature for 24 h, quenched with water (10.0 mL) and extracted with ethyl acetate (10.0 mL). The organic layer was dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to afford diethyl [3,5-dimethyl-4-(4'-hydroxybenzyl)phenoxy]methylphosphonate (0.22 g, 95%) as colorless oil:  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.11 (s, 1 H), 6.60-6.80 (m, 6 H), 4.35 (d,  $J$  = 14.7 Hz, 2 H), 4.11 (m, 4 H), 3.80 (s, 2 H), 2.15 (s, 6 H), 1.25 (t,  $J$  = 10.5 Hz, 2 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = acetone-hexanes (1:1);  $R_f$  = 0.40.

[0821] [3,5-Dimethyl-4-(4'-hydroxy-3'-iodobenzyl)phenoxy]methylphosphonic acid was prepared from diethyl [3,5-dimethyl-4-(4'-hydroxybenzyl)phenoxy]methylphosphonate according to the procedure described in compound 2 steps f and g:  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.27 (d,  $J$  = 2.4 Hz, 1 H), 6.83 (dd,  $J$  = 8.1, 2.1 Hz, 1 H), 6.76 (s, 2 H), 6.72 (d,  $J$  = 8.1 Hz, 1 H), 4.23 (d,  $J$  = 10.2 Hz, 2 H), 3.91 (s, 2 H), 2.23 (s, 6 H); LC-MS  $m/z$  = 449  $[\text{C}_{16}\text{H}_{18}\text{IO}_3\text{P} + \text{H}]^+$ ; Anal Calcd for  $(\text{C}_{16}\text{H}_{18}\text{IO}_3\text{P} + 0.7 \text{ H}_2\text{O})$ : C, 41.70; H, 4.24. Found: C, 41.73; H, 4.56.

## Example 35:

**Compound 35:** [3,5-dimethyl-4-(3'-carboxyl-4'-hydroxy-benzyl)phenoxy]methylphosphonic acid

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Step a:

[0822] To the suspension of NaH (3.25 g, 0.135 mol) in DMF (150 mL) was added 4-hydroxy-benzaldehyde (15.0 g, 0.123 mol) in DMF (10 mL) at 0 °C, 5 min. later the reaction mixture became a cake. The heterogeneous mixture was stirred at 0 °C for 30 min. MOMCl (9.96 g, 0.123 mol) was added slowly and the reaction mixture was allowed to warm up to r.t. After stirring at r.t. for 16 h, the volatiles were removed under vacuum. The residue was partitioned between ethyl acetate and water and the water layer was further extracted with ethyl acetate. The combined ethyl acetate extracts were dried over MgSO<sub>4</sub>, filtered and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate-hexanes;1:4) to afford 4-methoxymethoxy-benzaldehyde (19.0 g, 93%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.94 (s, 1H), 7.88 (m, 2H), 7.18 (m, 2H), 5.29 (s, 2H), 3.53 (s, 2H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:4); R<sub>f</sub> = 0.86.

Step b:

[0823] To a solution of (4-bromo-3,5-dimethyl-phenoxy)triisopropylsilane (8.0 g, 23.30 mmol) in THF (50 mL) was added a solution of n-butyllithium (2.5 M in THF, 90 mL) at -78 °C. The heterogeneous mixture was stirred at -78 °C for 1 h. A solution of 4-methoxymethoxy-benzaldehyde (3.09 g, 18.58 mmol) in THF (5 mL) was added and the mixture was stirred at -78 °C for 1 h then warmed up to r.t. The reaction was then diluted with ethyl acetate and water, the layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried (MgSO<sub>4</sub>), filtered and concentrated to afford crude (2,6-dimethyl-4-

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triisopropylsilyloxyphenyl)-(4-methoxymethoxyphenyl)methanol. Carried on to the next step without further purification.

Step c:

[0824] A degassed solution of crude (2,6-dimethyl-4-triisopropylsilyloxyphenyl)-(4-methoxymethoxyphenyl)methanol (12.0 g, 26.84 mmol) and Pd/C (1.2 g) in EtOAc/HOAc (19/1) was stirred under an atmosphere of hydrogen (1 atm) at r.t. After 5 h, the catalyst was filtered through a pad of Celite, rinsed with ethyl acetate and the combined filtrates concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate-hexanes;1:9) to afford 4-(2,6-dimethyl-4-triisopropylsilyloxybenzyl)-methoxymethoxybenzene (4.0 g, 41.5% for two steps):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.93 (s, 4H), 6.63 (s, 2H), 5.16 (s, 2H), 3.94 (s, 2H), 3.50 (m, 3H), 1.58 (s, 6H), 1.29 (m, 3H), 1.13 (m, 18H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:19);  $R_f$ = 0.80.

Step d:

[0825] To a solution of 4-(2,6-dimethyl-4-triisopropylsilyloxybenzyl)-methoxymethoxybenzene (2.0 g, 4.66 mmol) in ether was added TMEDA (1.05 mL, 6.99 mmol), followed by nBuLi (2.5 M in THF, 2.8 mL) at  $-20^\circ\text{C}$ . The reaction mixture was warmed up to  $0^\circ\text{C}$  and stirred for 1 h DMF (0.72 mL, 9.32 mmol) was then added and after stirring at  $0^\circ\text{C}$  for 2 h, the reaction mixture was quenched with a saturated solution of  $\text{NH}_4\text{Cl}$  and diluted with EtOAc. The water layer was extracted with EtOAc and the combined organic extracts were dried ( $\text{MgSO}_4$ ), filtered and concentrated to give the crude product 5-(2,6-dimethyl-4-triisopropylsilyloxybenzyl)-2-methoxymethoxybenzaldehyde (2.1 g, 98%):  $^1\text{H}$  NMR (300 MHz,  $d_6$ -DMSO):  $\delta$  10.33 (s, 1H), 7.24 (m, 3H), 6.58 (s, 2H), 5.31 (s, 2H), 3.91 (s, 2H), 3.33 (s, 6H), 1.23 (m, 3H), 1.06 (m, 18H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:9);  $R_f$ = 0.55.

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## Step e:

[0826] To a solution of 5-(2,6-dimethyl-4-triisopropylsilyloxybenzyl)-2-methoxymethoxy-benzaldehyde (1.4 g, 3.07 mmol) in THF (15 mL) was added TBAF (1 M, 3.68 mL) at 0 °C. After stirring at r.t. for 2 h, the reaction mixture was diluted with EtOAc and water. The water layer was extracted with EtOAc and the combined organic extracts were dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate-hexanes; 1:9) to afford 5-(4-hydroxy-2,6-dimethylbenzyl)-2-methoxymethoxybenzaldehyde (590 mg, 64% for two steps): <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 10.45 (s, 1H), 7.54 (s, 1H), 7.27 (m, 1H), 7.09 (m, 1H), 6.56 (s, 2H), 5.25 (s, 2H), 3.92 (s, 2H), 3.50 (s, 3H), 2.16 (s, 6H). TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:9); R<sub>f</sub> = 0.68.

## Step f:

[0827] To a solution of 5-(4-hydroxy-2,6-dimethylbenzyl)-2-methoxymethoxybenzaldehyde (590 mg, 1.97 mmol) in DMF (10 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (3.2 g, 9.83 mmol), followed by trifluoromethanesulfonic acid diethoxy-phosphorylmethyl ester (649 mg, 2.16 mmol) at r.t. After stirring at r.t. for 16 h, the reaction mixture was concentrated under reduced pressure and the residue was partitioned between EtOAc and water. The water layer was extracted with EtOAc and the combined organic extracts were dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate-hexanes; 1:1) to afford diethyl [4-(3'-formyl-4'-methoxymethoxybenzyl)-3,5-dimethylphenoxy] methylphosphonate (650 mg, 72%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 10.42 (s, 1H), 7.51 (s, 1H), 7.09 (m, 2H), 6.67 (s, 2H), 5.25 (s, 2H), 4.26 (m, 6H), 3.94 (s, 2H), 3.50 (s, 3H), 2.19 (s, 6H), 1.37 (m, 6H). TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:1); R<sub>f</sub> = 0.55.

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Step g:

[0828] To a solution of [4-(3'-formyl-4'-methoxymethoxybenzyl)-3,5-dimethylphenoxy]methylphosphonate (650 mg, 1.44 mmol) in THF (1.0 mL) at r.t. was added a solution of  $\text{NaH}_2\text{PO}_4$  (52 mg, 0.43 mmol) in water (0.2 mL), 30%  $\text{H}_2\text{O}_2$  (30%, 0.16 mL) followed by a solution of sodium chloride (245 mg, 2.17 mmol) in water (1.0 mL). After stirring at r.t. for 30 min., the reaction mixture was diluted with EtOAc and water. The water layer was extracted with EtOAc and the combined organic extracts were washed with water, brine, dried ( $\text{MgSO}_4$ ), filtered and concentrated to afford diethyl [3,5-dimethyl-4-(3'-carboxyl-4'-hydroxybenzyl)phenoxy]methylphosphonate as yellow solid (585 mg, 86.9%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.91 (m, 1H), 7.11 (m, 2H), 6.68 (s, 2H), 4.25 (m, 6H), 3.96 (s, 2H), 3.54 (s, 3H), 2.19 (s, 6H), 1.37 (m, 6H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = MeOH-ethyl acetate (1:9);  $R_f$  = 0.2.

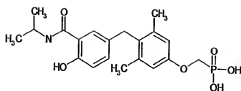
Step h:

[0829] To the solution of diethyl [3,5-dimethyl-4-(3'-carboxyl-4'-hydroxybenzyl)phenoxy]methylphosphonate (100 mg, 0.21 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added TMSBr (0.28 mL, 2.10 mmol) at r.t. After stirring at r.t. for 16 h, the reaction mixture was concentrated and the residue was suspended in MeOH. After stirring for 2 h, the volatiles were removed and the residue was azeotroped with  $\text{CH}_2\text{Cl}_2$  twice to provide [3,5-dimethyl-4-(3'-carboxyl-4'-hydroxybenzyl)phenoxy]methylphosphonic acid as a white solid (48 mg, 61.5%): mp.  $>200^\circ\text{C}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.38 (d,  $J$  = 2.1 Hz, 1H), 7.17 (m, 1H), 6.87 (d,  $J$  = 8.4 Hz, 1H), 6.74 (s, 2H), 4.06 (d,  $J$  = 10.2 Hz, 2H), 3.89 (s, 2H), 2.18 (s, 6H). mp  $>200$ , LC-MS  $m/z$  = 367 [ $\text{C}_{17}\text{H}_{19}\text{O}_7\text{P} + \text{H}$ ].<sup>+</sup>; Anal. Calcd for ( $\text{C}_{17}\text{H}_{19}\text{O}_7\text{P} + 0.4 \text{ H}_2\text{O}$ ): C, 54.67; H, 5.34. Found: C, 54.57; H, 5.60.

### Example 36:

**Compound 36:** [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylcarbamoylbenzyl)-phenoxy]methylphosphonic acid

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Step a:

[0830] To a solution of diethyl [3,5-dimethyl-4-(3'-carboxyl-4'-hydroxy-benzyl)phenoxy]methylphosphonate (compound 35, step f; 122 mg, 0.262 mmol) in DMF (5.0 mL) was added EDCI (60 mg, 0.314 mmol), HOAT (53 mg, 0.393 mmol), diisopropylethylamine (0.23 mL, 1.31 mmol) and isopropylamine (0.03 mL, 0.288 mmol). After stirring at r.t. for 16 h, the reaction mixture was concentrated under reduced pressure and the residue was partitioned between EtOAc and a saturated solution of NaHCO<sub>3</sub>. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with water, brine, dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate-hexanes; 1:1) to afford diethyl [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylcarbamoylbenzyl)-phenoxy]methylphosphonic acid as yellowish liquid (40 mg, 30%). TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:1); R<sub>f</sub> = 0.45.

Step b:

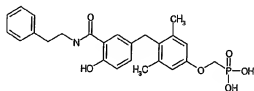
[0831] The title compound was prepared by the procedure described for the synthesis of compound 35, step f as an off-white solid (30 mg, 93.7%); mp.: 90 °C, dec; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.52 (d, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 1.5 Hz, 1H), 6.73(m, 4H), 4.14 (m, 1H), 4.06 (d, *J* = 10.2 Hz, 2H), 3.88 (s, 2H), 2.18 (s, 6H), 1.21 (d, *J* = 6.9 Hz, 6H). mp: decomposed at 90, LC-MS *m/z* = 408 [C<sub>20</sub>H<sub>26</sub>NO<sub>6</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>20</sub>H<sub>26</sub>NO<sub>6</sub>P + 0.26 acetone + 1.4 HBr): C, 46.58; H, 5.45; N, 2.61. Found: C, 46.49; H, 5.84; N, 2.93.



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## Example 37:

**Compound 37:** [3,5-dimethyl-4-(4'-hydroxy-3'-phenethylcarbamoylbenzyl)phenoxy]methylphosphonic acid



Step a:

[0832] 5-(2,6-dimethyl-4-triisopropylsilyloxybenzyl)-2-methoxymethoxy benzaldehyde (example 35; step e) was transformed into 5-(2,6-dimethyl-4-triisopropylsilyloxybenzyl)-2-methoxymethoxybenzoic acid by the procedure used for the synthesis of compound 35, step g: yellow solid (360 mg, 86.9%);  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.94 (s, 1H), 7.08 (m, 2H), 6.60 (s, 2H), 5.36 (s, 2H), 3.95 (s, 2H), 3.53 (s, 3H), 2.14 (s, 6H), 1.26 (m, 3H), 1.14 (m, 18H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = MeOH-ethyl acetate (1:9);  $R_f$  = 0.45.

Step b:

[0833] *N*-phenethyl-5-(2,6-dimethyl-4-triisopropylsilyloxybenzyl)-2-methoxymethoxybenzamide was prepared by the procedure used for the synthesis of compound 36, step a: colorless liquid (330 mg, 75%);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.05 (d,  $J$  = 2.4 Hz, 1H), 7.84 (m, 1H), 7.82 (m, 5H), 6.97 (d,  $J$  = 9.0 Hz, 1H), 6.64 (m, 1H), 6.61 (s, 2H), 5.01 (s, 2H), 3.97 (s, 2H), 3.82 (m, 2H), 3.30 (s, 3H), 2.97 (m, 2H), 2.18 (s, 6H), 1.28 (m, 3H), 1.14 (m, 18H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:1);  $R_f$  = 0.55.

Step c:

[0834] *N*-phenethyl-5-(2,6-dimethyl-4-hydroxybenzyl)-2-methoxymethoxy benzamide was prepared by the procedure used for the synthesis of compound

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35, step c: (170 mg, 70%); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:1);  $R_f = 0.45$ .

Step d:

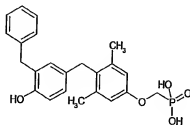
[0835] Diethyl[3,5-dimethyl-4-(4'-methoxymethoxy-3'-phenethylcarbamoyl benzyl)phenoxy]methylphosphonate was prepared by the procedure used for the synthesis of compound 35, step f: (185 mg, 80%);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.98 (d,  $J = 2.1$  Hz, 1H), 7.85 (m, 1H), 7.32 (m, 5H), 7.01 (d,  $J = 5.4$  Hz, 1H), 6.91 (m, 1H), 6.69 (s, 2H), 4.29 (m, 4H), 3.98 (s, 2H), 3.81 (m, 2H), 3.31 (s, 3H), 2.96 (m, 2H), 2.22 (s, 6H), 1.41 (m, 6H). TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:1);  $R_f = 0.52$ .

Step e:

[0836] The title compound was prepared by the procedure used for the synthesis of compound 35, step h: white solid (40 mg, 48.8%); mp.: 100 °C, dec;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.85 (m, 1H), 7.67 (d,  $J = 2.1$  Hz, 1H), 7.32 (m, 5H), 6.86 (m, 2H), 6.78 (s, 2H), 4.10 (d,  $J = 10.5$  Hz, 2H), 3.91 (s, 2H), 3.57 (m, 2H), 2.92 (m, 2H), 2.24 (s, 6H). mp: decomposed at 100, LC-MS  $m/z = 470$  [ $\text{C}_{25}\text{H}_{28}\text{NO}_6\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{25}\text{H}_{28}\text{NO}_6\text{P} + 0.9$  HBr): C, 55.37; H, 5.37; N,

### Example 38:

**Compound 38:** [4-(3'-benzyl-4'-hydroxy-benzyl)-3,5-dimethylphenoxy] methylphosphonic acid



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## Step a:

[0837] To a stirring solution of bromobenzene (0.45 g, 2.89 mmol) in THF (20 mL) at  $-78^{\circ}\text{C}$  was added *n*-BuLi (1.16 mL, 2.5 M in hexanes). The mixture was stirred at  $-78^{\circ}\text{C}$  for 1 h and a solution of 5-(2,6-dimethyl-4-triisopropylsilyloxybenzyl)-2-methoxymethoxybenzaldehyde (example 35; step e, 1.2 g, 2.63 mmol) was added. The reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 1 h, allowed to warm to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  and diluted with diethyl ether. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to afford [5-(2,6-dimethyl-4-triisopropylsilyloxybenzyl)-2-methoxymethoxy-phenyl]-phenyl-methanol as a yellow oil (1.4 g, 99.6%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.23 (m, 6 H), 6.85 (d,  $J = 8.8$  Hz, 1 H), 6.68 (m, 1 H), 6.56 (s, 2 H), 5.92 (d,  $J = 4.0$  Hz, 1 H), 5.62 (d,  $J = 4.0$  Hz, 1 H), 5.10 (q,  $J = 4.0$  Hz, 2 H), 3.84 (s, 2 H), 3.23 (s, 3 H), 2.11 (s, 6 H), 1.23 (m, 3 H), 1.06 (d,  $J = 6.4$  Hz, 18 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 15% ethyl acetate in hexanes;  $R_f = 0.50$ .

## Step b:

[0838] To a solution of [5-(2,6-dimethyl-4-triisopropylsilyloxybenzyl)-2-methoxymethoxy-phenyl]-phenyl-methanol (1.4 g, 2.6 mmol) in ethyl acetate (20 mL) and acetic acid (1.5 mL) was added Pd/C (0.15 g). The mixture was stirred under  $\text{H}_2$  atmosphere for 16 h. The mixture was filtered through a celite plug. The solvent was removed under reduced pressure. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (26 mL), ethyl-diisopropyl-amine (0.69 mL, 3.95 mmol) and chloromethyl methyl ether (0.26 mL, 3.42 mmol) were added. The reaction mixture was refluxed for 16 h and quenched with water. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (15:75) to afford [4-(3'-benzyl-4'-methoxymethoxy-benzyl)-3,5-dimethyl-phenoxy]-triisopropylsilane as an oil (0.9 g, 66%):  $^1\text{H}$ -NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.20 (m, 5 H), 6.90 (d,  $J = 8.4$  Hz, 1 H), 6.79 (s, 1 H), 6.70 (m, 1 H), 6.54 (s, 2 H), 5.12 (s, 2 H), 3.83 (s,

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2 H), 3.81 (s, 2 H), 3.25 (s, 3 H), 2.09 (s, 6 H), 1.23 (m, 3 H), 1.06 (d,  $J = 6.6$  Hz, 18 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 15% ethyl acetate in hexanes;  $R_f = 0.66$ .

Step c:

[0839] To a stirring solution of [4-(3'-benzyl-4'-methoxymethoxy-benzyl)-3,5-dimethyl-phenoxy]-triisopropylsilane (0.9 g, 1.73 mmol) in THF (20 mL) at room temperature was added tetrabutylammonium fluoride (2.3 mL, 1.0 M in THF). The reaction mixture was stirred at room temperature for 1 h, diluted with diethyl ether and washed with water (30 mLx2). The solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:1) to afford 4-(3'-benzyl-4'-methoxymethoxy-benzyl)-3,5-dimethyl-phenol as a light yellow oil (0.6 g, 86%):  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  8.98 (s, 1 H), 7.16 (m, 5 H), 6.87 (m, 2 H), 6.70 (m, 1 H), 6.43 (s, 2 H), 5.12 (s, 2 H), 3.85 (s, 2 H), 3.76 (s, 2 H), 3.24 (s, 3 H), 2.06 (s, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 20% ethyl acetate in hexanes;  $R_f = 0.34$ .

Step d:

[0840] Diethyl [4-(3'-benzyl-4'-methoxymethoxy-benzyl)-3,5-dimethyl-phenoxy]methylphosphonate was prepared by the procedure used for the synthesis of compound 35, step f as a light yellow oil (0.09 g, 64%):  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  7.22 (m, 5 H), 6.87 (m, 2 H), 6.70 (m, 3 H), 5.12 (s, 2 H), 4.35 (d,  $J = 10$  Hz, 2 H), 4.11 (m, 4 H), 3.85 (s, 2 H), 3.82 (s, 2 H), 3.24 (s, 3 H), 2.13 (s, 6 H), 1.25 (t,  $J = 7$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 40% ethyl acetate in hexanes;  $R_f = 0.27$ .

Step e:

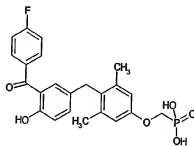
[0841] The title compound was prepared by the procedure used for the synthesis of compound 35, step h as a white foam (32 mg, 44%):  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  9.14 (s, 1 H), 7.21 (m, 5 H), 6.67 (m, 4 H), 6.56 (m,

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1 H), 4.02 (d,  $J = 10.2$  Hz, 2 H), 3.78 (s, 2 H), 3.75 (s, 2 H), 2.12 (s, 6 H); LC-MS  $m/z = 413$  [ $C_{23}H_{25}O_5P + H$ ] $^+$ ; Anal Calcd for ( $C_{23}H_{25}O_5P + 0.2 Et_2O + 0.6 H_2O$ ): C, 65.26; H, 6.49. Found: C, 65.07; H, 6.38.

### Example 39:

**Compound 39:** [3,5-dimethyl-4-[3'-(4-fluoro-benzoyl)-4'-hydroxy-benzyl]phenoxy]methylphosphonic acid



Step a:

[0842] [5-(2,6-dimethyl-4-triisopropylsilyloxy-benzyl)-2-methoxymethoxy-phenyl]-(4-fluoro-phenyl)-methanol was prepared by the procedure used for the synthesis of example 38, step a as an oil (0.68 g, 56%):  $^1H$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  7.26 (m, 3 H), 7.06 (m, 2 H), 6.85 (d,  $J = 8.4$  Hz, 1 H), 6.71 (m, 1 H), 6.56 (s, 2 H), 5.91 (d,  $J = 4.0$  Hz, 1 H), 5.68 (d,  $J = 4.0$  Hz, 1 H), 5.10 (q,  $J = 3.4$  Hz, 2 H), 3.84 (s, 2 H), 3.22 (s, 3 H), 2.11 (s, 6 H), 1.23 (m, 3 H), 1.06 (d,  $J = 6.2$  Hz, 18 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 15% ethyl acetate in hexanes;  $R_f = 0.26$ .

Step b:

[0843] To a stirring solution of [5-(2,6-dimethyl-4-triisopropylsilyloxy-benzyl)-2-methoxymethoxy-phenyl]-(4-fluoro-phenyl)-methanol (0.68 g, 1.2 mmol) in dichloromethane (25 mL) at 0 °C was added Dess-Martin periodinane (3.9 mL, 0.48 M solution in  $CH_2Cl_2$ ). The reaction mixture was stirred at room temperature for 4 h, concentrated, diluted with ethyl acetate. To the solution was added a solution of  $Na_2S_2O_3$  pentahydrate (50 mg) in 60

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mL saturated  $\text{NaHCO}_3$ . After 15 min, the organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to afford crude 5-(2,6-dimethyl-4-triisopropylsilyloxy-benzyl)-(4-fluorobenzoyl)-2-methoxymethoxy-phenyl as an oil (0.68 g, 100%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.72 (m, 2 H), 7.33 (m, 2 H), 7.12 (m, 2 H), 6.86 (s, 1 H), 6.56 (s, 2 H), 5.04 (s, 2 H), 3.92 (s, 2 H), 3.14 (s, 3 H), 2.13 (s, 6 H), 1.21 (m, 3 H), 1.03 (d,  $J = 6.2$  Hz, 18 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 20% ethyl acetate in hexanes;  $R_f = 0.26$ .

Step c:

[0844] To a stirring solution of 4-(2',6'-dimethyl-4'-triisopropylsilyloxy-benzyl)-2-(4-fluorobenzoyl)-phenol was prepared by the procedure used for the synthesis of example 35 step c as a white solid (0.42 g, 86%): mp 140–142 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.05 (s, 1 H), 7.78 (m, 2 H), 7.36 (m, 2 H), 7.13 (m, 2 H), 6.95 (d,  $J = 1.5$  Hz, 1 H), 6.47 (s, 2 H), 5.05 (s, 2 H), 3.90 (s, 2 H), 3.15 (s, 3 H), 2.12 (s, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 20% ethyl acetate in hexanes;  $R_f = 0.63$ .

Step d:

[0845] Diethyl[3,5-dimethyl-4-[3'-(4-fluoro-benzoyl)-4'-hydroxy-benzyl]phenoxy]methylphosphonate was prepared by the procedure used for the synthesis of example 35 step f as a light yellow oil (0.054 g, 19%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.76 (m, 2 H), 7.36 (m, 2 H), 7.13 (m, 2 H), 6.94 (d,  $J = 1.5$  Hz, 1 H), 6.77 (s, 2 H), 5.05 (s, 2 H), 4.36 (d,  $J = 9.6$  Hz, 2 H), 4.11 (m, 4 H), 3.95 (s, 2 H), 3.15 (s, 3 H), 2.20 (s, 6 H), 1.25 (m, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 67% ethyl acetate in hexanes;  $R_f = 0.37$ .

Step d:

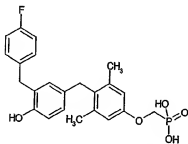
[0846] The title compound was prepared by the procedure used for the synthesis of example 35 step h as a yellow foam (22 mg, 50%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  10.14 (s, 1 H), 7.74 (m, 2 H), 7.31 (m, 2 H), 7.03 (m, 1

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H), 6.92 (m, 2 H), 6.69 (s, 2 H), 4.02 (d,  $J = 10.6$  Hz, 2 H), 3.87 (s, 2 H), 2.16 (s, 6 H); LC-MS  $m/z = 445$  [ $C_{23}H_{22}FO_6P + H$ ] $^+$ ; Anal Calcd for ( $C_{23}H_{22}FO_6P + 0.2 Et_2O + 0.3 CF_3COOH$ ): C, 59.39; H, 4.96. Found: C, 59.62; H, 4.64.

### Example 40:

**Compound 40:** [3,5-dimethyl-4-[3'-(4-fluoro-benzyl)-4'-hydroxy-benzyl]phenoxy]methylphosphonic acid



Step a:

[0847] To a stirring solution of diethyl [3,5-dimethyl-4-[3'-(4-fluoro-benzyl)-4'-hydroxy-benzyl]phenoxy]methylphosphonic acid (0.13 g, 0.24 mmol) in MeOH (8 mL) at 0 °C was added  $NaBH_4$  (90 mg, 2.4 mmol). The reaction mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was dried over  $Na_2SO_4$ , filtered and concentrated under reduced pressure to afford diethyl [3,5-dimethyl-4-[3'-(4-fluorophenyl-hydroxymethyl)-4'-hydroxy-benzyl]phenoxy]methylphosphonic acid as an oil (0.13 g, 100%). This crude product was dissolved in  $CH_2Cl_2$  (10 mL) and  $Et_3SiH$  (0.38 mL, 2.4 mmol) and TFA (0.18 mL, 2.4 mmol) were added. The reaction mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and saturated  $NaHCO_3$ . The organic layer was dried over  $Na_2SO_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate to afford diethyl [3,5-dimethyl-4-[3'-(4-fluoro-benzyl)-4'-hydroxy-benzyl]phenoxy]methylphosphonate as an oil (80 mg, 69%);  $^1H$  NMR (200 MHz,  $DMSO-d_6$ ):  $\delta$  9.18 (s, 1 H), 7.13 (m, 4 H), 6.67 (m, 5 H),

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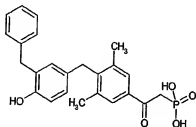
4.33 (d,  $J = 10$  Hz, 2 H), 4.11 (m, 4H), 3.76 (s, 4 H), 2.12 (s, 6H), 1.25 (t,  $J = 7$  Hz, 6 H). TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate;  $R_f = 0.5$ .

Step b:

[0848] The title compound was prepared by the procedure used for the synthesis of example 35 step h as a yellow solid (60 mg, 85%):  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  9.11 (s, 1 H), 7.13 (m, 4 H), 6.63 (m, 5 H), 4.01 (d,  $J = 10.2$  Hz, 2 H), 3.76 (s, 4 H), 2.12 (s, 6 H); LC-MS  $m/z = 431$  [ $\text{C}_{23}\text{H}_{24}\text{FO}_3\text{P} + \text{H}$ ] $^+$ ; Anal Calcd for ( $\text{C}_{23}\text{H}_{24}\text{FO}_3\text{P} + 0.6 \text{ H}_2\text{O} + 0.2 \text{ Et}_2\text{O}$ ): C, 62.68; H, 6.01. Found: C, 62.31; H, 6.16; mp: 169 - 171 °C.

#### Example 41:

**Compound 41:** [3,5-dimethyl-4-[3'-benzyl-4'-hydroxy-benzyl]benzoyl] methylphosphonic acid



Step a:

[0849] To a solution of 4-(3'-benzyl-4'-methoxymethoxy-benzyl)-3,5-dimethyl-phenol (example 38, step c, 0.5 g, 1.38 mmol) and DMAP (0.67 g, 5.52 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) at 0 °C was slowly added trifluoromethanesulfonyl anhydride (0.35 mL, 2.1 mmol). The reaction mixture was stirred at 0 °C for 2 h and quenched by water (10 mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to afford 4-(3'-benzyl-4'-methoxymethoxy-benzyl)-3,5-dimethyl-phenyl trifluoromethanesulfonate as an oil (0.5 g, 73%):  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  7.14 – 7.28 (m, 7 H), 6.94 (d,  $J = 8.4$  Hz, 1 H), 6.85 (d,  $J = 2.4$  Hz, 1 H), 6.70 (m, 1 H), 5.15 (s, 2 H), 3.94 (s, 2 H), 3.88 (s, 2 H), 3.27 (s, 3



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H), 2.24 (s, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (15:75);  $R_f$  = 0.55.

Step b:

[0850] To a solution of 4-(3'-benzyl-4'-methoxymethoxy-benzyl)-3,5-dimethyl-phenyl trifluoromethanesulfonate (0.5 g, 1 mmol) in DMF (8 mL) in a bomb apparatus was added MeOH (0.82 mL, 20 mmol), Pd(OAc)<sub>2</sub> (23 mg, 0.1 mmol), bis-(diphenylphosphino)propane (42 mg, 0.1 mmol) and TEA (0.28 mL, 2 mmol). 60 psi of CO was then infused and the reaction mixture was stirred at 90 °C for 16 h. The cooled bomb was vented and the reaction mixture was poured into cold 1N HCl, extracted with EtOAc twice, the combined EtOAc were washed with brine, dried over MgSO<sub>4</sub>, filtrated and concentrated. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (15:75) to afford methyl 4-(3'-benzyl-4'-methoxymethoxy-benzyl)-3,5-dimethyl-benzoate as a yellow oil (360 mg, 88%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.66 (s, 2 H), 7.16 (m, 5 H), 6.90 (m, 2 H), 6.71 (m, 1 H), 5.15 (s, 2 H), 3.98 (s, 2 H), 3.87 (s, 2 H), 3.85 (s, 3 H), 3.26 (s, 3H), 2.25 (s, 6H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (15:75);  $R_f$  = 0.50.

Step c:

[0851] To a stirring solution of diethyl methylphosphonate (0.39 mL, 2.67 mmol) in THF (10 mL) at -78 °C was added *n*-BuLi (2.5 M in hexanes, 1.07 mL), the reaction mixture was stirred at -78 °C for 1 h, then methyl 4-(3'-benzyl-4'-methoxymethoxy-benzyl)-3,5-dimethyl-benzoate (360 mg, 0.89 mmol) in THF (10 mL) was added at the same temperature. The reaction mixture was stirred at -78 °C for 1.5 h, then at room temperature for 1 h. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl and diluted with diethyl ether. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate to afford diethyl [3,5-dimethyl-4-[3'-benzyl-4'-hydroxy-benzyl]benzoyl]methylphosphonate as a light yellow oil

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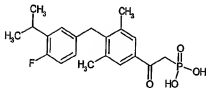
(350 mg, 75%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.72 (s, 2 H), 7.16 (m, 5 H), 6.92 (m, 2 H), 6.71 (m, 1 H), 5.14 (s, 2 H), 4.04 (m, 6 H), 3.99 (s, 2 H), 3.82 (d,  $J = 22.2$  Hz, 2 H), 3.26 (s, 3H), 2.27 (s, 6H), 1.19 (t,  $J = 7.5$  Hz, 6 H). TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (2:1);  $R_f = 0.35$ .

Step d:

[0852] The title compound was prepared by the procedure described for the synthesis of example 35, step h as a white foam (55 mg, 88%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.21 (s, 1 H), 7.66 (s, 2 H), 7.21 (m, 5 H), 6.65 (m, 2 H), 6.55 (m, 1 H), 3.89 (s, 2 H), 3.79 (s, 2 H), 3.45 (d,  $J = 22.8$  Hz, 2 H), 2.16 (s, 6 H); LC-MS  $m/z = 425$  [ $\text{C}_{24}\text{H}_{25}\text{O}_5\text{P} + \text{H}$ ] $^+$ ; Anal Calcd for ( $\text{C}_{24}\text{H}_{25}\text{O}_5\text{P} + 1.6 \text{H}_2\text{O}$ ): C, 63.60; H, 6.27. Found: C, 63.87; H, 6.43.

[0853] Using the appropriate starting material, compounds 41-1 to 41-3 were prepared in an analogous manner to that described for the synthesis of compound 41.

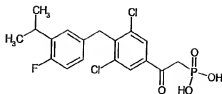
**Compound 41-1:** 2-[3,5-dimethyl-4-(4'-fluoro-3'-*iso*-propyl-benzyl)phenyl]-2-oxo-ethylphosphonic acid



[0854] The title compound was prepared from 3,5-dimethyl-4-(4'-fluoro-3'-*iso*-propyl-benzyl)-phenol (compound 27, step e) by the procedure described for the synthesis of compound 41 as a white solid (106 mg, 81.5%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.70 (s, 2H), 7.10 (m, 1H), 6.98 (m, 1H), 6.65 (m, 1H), 4.00 (s, 2H), 3.48 (d,  $J = 22.4$  Hz, 2H), 3.09 (m, 1H), 2.26 (s, 6H), 1.17 (d,  $J = 7.0$  Hz, 6H). mp = 138-140, LC-MS  $m/z = 379$  [ $\text{C}_{20}\text{H}_{24}\text{FO}_4\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{20}\text{H}_{24}\text{FO}_4\text{P}$ ): C, 63.49; H, 6.39. Found: C, 63.40; H, 6.63.

**Compound 41-3:** 2-[3,5-dichloro-4-(4-fluoro-*iso*-propyl-benzyl)-phenyl]-2-oxo-ethylphosphonic acid

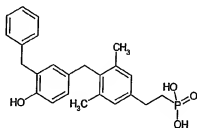
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[0855] 3,5-Dichloro-4-(4-fluoro-3-*iso*-propyl-benzyl)-phenol, intermediate for the synthesis of compound 27-2, was transformed into the title compound by the procedure described for the synthesis of compound 41 to give a white solid (65 mg, 82%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.08 (s, 2H), 7.25 (m, 1H), 7.05 (m, 1H), 6.90 (m, 1H), 4.32 (s, 2H), 3.60 (d,  $J = 22.5$  Hz, 2H), 3.12 (m, 1H), 1.20 (d,  $J = 6.9$  Hz, 6H). mp = 132~134, LC-MS  $m/z$  = 417  $[\text{C}_{18}\text{H}_{18}\text{Cl}_2\text{FO}_4\text{P} + \text{H}]^+$ ; Anal. Calcd for  $(\text{C}_{18}\text{H}_{18}\text{Cl}_2\text{FO}_4\text{P})$ : C, 51.57; H, 4.33. Found: C, 51.37; H, 4.65.

#### Example 42:

**Compound 42:** 2-[3,5-dimethyl-4-[3'-benzyl-4'-hydroxy-benzyl]phenyl]-ethylphosphonic acid



Step a:

[0856] To a stirring solution of diethyl [3,5-dimethyl-4-[3'-benzyl-4'-hydroxy-benzyl]benzoyl]methylphosphonate (example 41, step c, 0.27 g, 0.52 mmol) in MeOH (10 mL) at 0 °C was added  $\text{NaBH}_4$  (78 mg, 2.1 mmol). The reaction mixture was stirred at room temperature for 4 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to afford diethyl 2-[4-(3'-benzyl-4'-

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methoxymethoxy-benzyl)-3,5-dimethyl-phenyl]-2-hydroxy-ethyl-phosphonate as an oil (0.27 g, 100%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.18 (m, 5 H), 7.03 (s, 2 H), 6.93 (m, 2 H), 6.70 (m, 1 H), 5.39 (d,  $J = 4.5$  Hz, 1 H), 5.14 (s, 2 H), 4.80 (m, 1 H), 3.85 (m, 8 H), 3.26 (s, 3H), 2.18 (s, 6H), 1.19 (m, 6 H). TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (2:1);  $R_f = 0.29$ .

Step b:

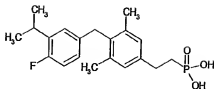
[0857] To a stirring solution of diethyl 2-[4-(3'-benzyl-4'-methoxymethoxy-benzyl)-3,5-dimethyl-phenyl]-2-hydroxy-ethyl-phosphonate (0.24 g, 0.46 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at room temperature was added  $\text{Et}_3\text{SiH}$  (0.34 mL, 2.1 mmol) and TFA (0.4 mL, 5.4 mmol). The reaction mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and saturated  $\text{NaHCO}_3$ . The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (3:1) to afford 2-[4-(3'-benzyl-4'-hydroxy-benzyl)-3,5-dimethyl-phenyl]ethylphosphonate as an oil (55 mg, 26%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.16 (s, 1 H), 7.22 (m, 5 H), 6.91 (s, 2 H), 6.76 (s, 1 H), 6.62 (m, 2 H), 4.00 (m, 4 H), 3.80 (s, 4 H), 2.68 (m, 2 H), 2.14 (s, 6H), 2.06 (m, 2H), 1.23 (m, 6 H). TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (2:1);  $R_f = 0.33$ .

Step c:

[0858] The title compound was prepared by the procedure described for the synthesis of example 35, step h as a light yellow solid (28 mg, 58%): mp: 168–170 °C;  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.11 (s, 1 H), 7.19 (m, 5 H), 6.85 (s, 2 H), 6.63 (m, 3 H), 3.77 (s, 4 H), 2.66 (m, 2 H), 2.12 (s, 6 H), 1.76 (m, 2 H); LC-MS  $m/z = 411$  [ $\text{C}_{24}\text{H}_{27}\text{O}_4\text{P} + \text{H}$ ] $^+$ ; Anal Calcd for ( $\text{C}_{24}\text{H}_{27}\text{O}_4\text{P} + 1.6 \text{ H}_2\text{O}$ ): C, 68.14; H, 6.77. Found: C, 68.19; H, 6.55;.

**Compound 42-1:** 2-[3,5-dimethyl-4-(4'-fluoro-3'-*iso*-propyl-benzyl)phenyl]ethylphosphonic acid

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Step a:

[0859] Intermediate diethyl 2-[3,5-dimethyl-4-(4'-fluoro-3'-*iso*-propyl-benzyl)phenyl]-2-oxo-ethylphosphonate for the synthesis of compound 41-1 was transformed into diethyl 2-[3,5-dimethyl-4-(4'-fluoro-3'-*iso*-propyl-benzyl)phenyl]-2-hydroxy-ethylphosphonate by the procedure described for the synthesis of compound 42, step a to give a yellow liquid (580 mg, 96.2%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.12 (s, 2H), 6.99 (m, 1H), 6.84 (m, 1H), 6.66 (m, 1H), 5.09 (s, 1H), 4.19 (m, 4H), 4.01 (s, 1H), 3.18 (m, 1H), 2.22 (s, 6H), 2.20 (m, 2H), 1.36 (m, 6H), 1.25 (d,  $J = 6.4$  Hz, 6H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (4:1);  $R_f = 0.58$ .

Step b:

[0860] A degassed solution of diethyl 2-[3,5-dimethyl-4-(4'-fluoro-3'-*iso*-propyl-benzyl)phenyl]-2-hydroxy-ethylphosphonate (500 mg, 1.15 mmol) and Pd/C (50 mg) in EtOH/HOAc(19/1) was stirred under 1 atmosphere of hydrogen at r.t. After 5h, the catalyst was filtered through a pad of celite and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate-hexanes; 9:1) to afford diethyl 2-[3,5-dimethyl-4-(4'-fluoro-3'-*iso*-propyl-benzyl)phenyl]ethylphosphonate (450 mg, 93.5%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.99 (s, 1H), 6.98 (s, 2H), 6.88 (m, 1H), 6.66 (m, 1H), 4.65 (m, 4H), 3.99 (s, 2H), 3.19 (m, 1H), 2.88 (m, 2H), 2.24 (s, 6H), 2.10 (m, 2H), 1.51 (m, 6H), 1.25 (d,  $J = 6.9$  Hz, 6H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:1);  $R_f = 0.53$ .

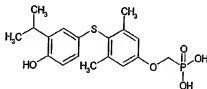
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Step c:

[0861] Diethyl-2-[3,5-dimethyl-4-(4'-fluoro-3'-*iso*-propyl-benzyl)phenyl]ethylphosphonate was transformed into the title compound by the procedure described for the synthesis of compound 35, step h to give a white solid (60 mg, 35%):  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  7.09 (m, 1H), 6.98 (m, 1H), 6.92 (s, 2H), 6.66 (m, 1H), 3.94 (s, 2H), 3.95 (s, 2H), 3.11 (m, 1H), 2.70 (m, 2H), 2.18 (s, 6H), 1.80 (m, 2H), 1.19 (d,  $J = 7.2$  Hz, 6H). mp = 116~118, LC-MS  $m/z = 365$  [ $\text{C}_{20}\text{H}_{26}\text{FO}_3\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{20}\text{H}_{26}\text{FO}_3\text{P}$ ): C, 65.92; H, 7.19. Found: C, 65.68; H, 7.19.

## Example 43

**Compound 43:** [3,5-dimethyl-4-S-[(4'-hydroxy-3'-*iso*-propylphenyl)sulfanyl]phenoxy]methylphosphonate:



Step a:

[0862] A mixture of 3,5-Dimethyl-4-iodophenol (2.0 g, 8.06mmol), potassium carbonate (3.33 g, 24.2 mmol) and methyl iodide (602  $\mu\text{L}$ , 9.67 mmol) in DMF (20 mL) under a nitrogen atmosphere was heated at 65 C, with stirring for 16 hours. The cooled reaction was diluted with ethyl acetate (50 mL), filtered into a sep-funnel and washed with water (2x 25mL) then brine (25 mL). The organics were dried over sodium sulfate, filtered and the solvent removed under reduced pressure to give (1.68 g, 79%);  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  6.79(s, 2H), 3.72(s, 3H), 2.37(s, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 5% ethyl acetate in hexane;  $R_f = 0.47$ .

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Step b:

[0863] Copper iodine (70 mg, 0.37 mmol), neocuprine (80 mg, 0.37 mmol) and potassium *t*-butoxide (470 mg, 4.05 mmol) were added in this order to a solution of 4-methoxy-3-*iso*-propyl-thiophenol (U.S. 6,747,048 B2, 600mg, 2.3 mmol) and 3,5-dimethyl-4-iodoanisole (678 mg, 3.72 mmol) in toluene (10mL). After refluxing overnight, the cooled reaction mixture was poured into ethyl acetate (50 mL) and washed twice with 1 N HCl then brine. The organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate 100:0 to 40:1) to give 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxyphenylsulfanyl)anisole (0.358 g, 49%); <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 6.87-6.80(m, 4H), 6.56(m, 1H), 3.76(s, 3H), 3.71(s, 3H), 3.15(m, 1H), 2.34(s, 6H), 1.06(d, 6H, *J* = 7Hz); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 25% ethyl acetate in hexane; R<sub>f</sub> = 0.36

Step c:

[0864] 3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propyl-phenylsulfanyl)phenol was prepared from 2,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxy-phenylsulfanyl) anisole according to the procedure described in example 8, step d. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.58(bs, 1H), 9.21(bs, 1H), 6.77(m, 1H), 6.63(m, 3H), 6.46(dd, 1H, *J* = 2.7 Hz and *J* = 8.1 Hz), 3.09(m, 1H), 2.28(s, 6H), 1.06(d, 6H, *J* = 7.2 Hz); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate 25% in hexane; R<sub>f</sub> = 0.12

Step d:

[0865] Diethyl[3,5-Dimethyl-4-(4'-hydroxy-3'-*iso*-propyl-phenylsulfanyl)-phenoxy]methyl phosphonate was prepared according to the procedure described in compound 8, step e: <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.26(s, 1H), 6.92(s, 2H), 6.81(d, 1H, *J* = 2.4 Hz), 6.65(d, 1H, *J* = 8.4 Hz), 6.47(dd, 1H, *J* = 2.1 Hz and *J* = 8 Hz), 4.42(d, 2H, *J* = 10 Hz), 4.11(m, 4H), 3.10(m, 1H), 2.35(s, 6H), 1.25(m, 6H), 1.06(d, 6H, *J* = 2.9 Hz); TLC conditions:

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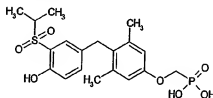
Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate 50% in hexane;  
 $R_f = 0.12$

Step e:

[0866] The title compound was prepared according to the procedure described in compound 8, step f:  $^1\text{H NMR}$  (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.22 (s, 1H), 6.88 (s, 2H), 6.81 (d,  $J = 2.1$  Hz, 1H), 6.64 (d,  $J = 8.4$  Hz, 1H), 6.46 (dd,  $J = 2$  Hz and  $J = 8.2$  Hz, 1H), 4.08 (d,  $J = 10.2$  Hz, 2H), 3.10 (m, 1H), 2.34 (s, 6H), 1.07 (d,  $J = 6.6$  Hz, 6H z); LC-MS  $m/z = 381$  [ $\text{C}_{18}\text{H}_{23}\text{O}_5\text{PS}^-$  H] $^-$ ; TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = IPA/ $\text{NH}_4\text{OH}/\text{H}_2\text{O}$  [7:1:2];  $R_f = 0.53$ ; HPLC, YMC Pack ODS-AQ, AQ 302, 150mm x 4.6 mm, S 5  $\mu\text{m}$ , 12nm, flow 2 mL/min, solvent A: 0.05% TFA aqueous, Solvent B: acetonitrile/0.05%TFA, Gradient 20% B to 70% B in 13min – hold 1 min at 70%B – gradient to 100%B in 6 min.  $R_t=10.23$  min.

#### Example 44:

**Compound 44:** [3,5-dimethyl-4-[4'-hydroxy-3'-(*iso*-propylsulfonyl)benzyl]phenoxy]methylphosphonic acid



Step a:

[0867] Triisopropyl-[3,5-dimethyl-4-(4'-methoxymethoxy-3'-(*iso*-propyl sulfonyl)benzyl)-phenoxy]silane was synthesized according to the procedure described in example 35, step d using di-*iso*-propyl disulfide as the electrophile. The product of this reaction was carried in the next step as a mixture of desired product and starting material triisopropyl-[3,5-dimethyl-4-(4'-methoxymethoxybenzyl)-phenoxy]silane:  $^1\text{H NMR}$  (200 MHz,  $\text{DMSO}-d_6$ ):



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$\delta$  1.15 (d,  $J = 6.4$  Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 5% ethyl acetate in hexane;  $R_f = 0.32$

Step b:

[0868] 3,5-Dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylsulfanylbenzyl)phenol was prepared according to the procedure described in example 35, step e. The product of this reaction was carried on as a mixture of desired product and 3,5-dimethyl 4-(4'-methoxymethoxybenzyl)phenol:  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  1.16 (d,  $J = 9.9$  Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 5% ethyl acetate in hexane;  $R_f = 0.25$

Step c:

[0869] Diethyl-[3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylsulfanylbenzyl)phenoxy]methylphosphonate was prepared according to the procedure described in example 8, step e and carried on as a mixture of desired product and diethyl [3,5-dimethyl 4-(4'-methoxymethoxybenzyl)phenoxy]methylphosphonate:  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  4.36 (d, 2H,  $J = 15$  Hz), 4.11 (m, 4H), 1.26 (t, 6H,  $J = 10.8$  Hz), 1.16 (d, 6H,  $J = 9.9$  Hz); LC-MS  $m/z = 465$  [ $\text{C}_{23}\text{H}_{36}\text{O}_6\text{PS} + \text{H}$ ] $^+$ ; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 50% ethyl acetate in hexane;  $R_f = 0.12$

Step d:

[0870] A mixture diethyl [3,5-dimethyl 4-(4'-methoxymethoxy-3'-*iso*-propylsulfanylbenzyl)phenoxy]methylphosphonate (0.200g, 0.402mmol), saturated sodium bicarbonate (1 ml) and *m*CPBA 50%-60% (0.173 g, 1.01 mmol) in dichloromethane (5 mL) was stirred overnight at room temperature. The layers were separated and the organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (2000  $\mu\text{m}$ , 5% hexanes in ethyl acetate) to give diethyl [3,5-dimethyl-4-[4'-methoxymethoxy-3'-(*iso*-propyl sulfonyl)benzyl]phenoxy]methylphosphonate (0.090 g, 42%);  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.42 (s, 1H), 7.24 (s, 2H), 6.77 (s, 2H), 5.32 (s, 2H), 4.36 (d,  $J = 10$  Hz, 2H), 4.11

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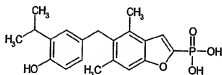
(m, 4H), 3.96 (s, 2H), 3.69 (m, 1H), 3.39 (s, 3H), 2.16 (s, 6H), 1.26 (t,  $J = 7$  Hz, 6H), 1.12 (d,  $J = 7$  Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate;  $R_f = 0.28$

Step c:

[0871] The title compound was prepared according to the described for example 8, step f (0.057 g, 82);  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  10.89 (bs, 1H), 7.31 (s, 1H), 7.12 (dd,  $J = 5.8, 2.2$  Hz, 1H z), 6.93 (d,  $J = 8$  Hz, 1H z), 6.72 (s, 2H), 4.04 (d,  $J = 10.2$  Hz, 2H z), 3.89 (s, 2H), 3.64 (m, 1H), 2.15 (s, 6H), 1.11 (d,  $J = 7$  Hz, 6H); LC-MS  $m/z = 427$  [ $\text{C}_{19}\text{H}_{25}\text{O}_7\text{PS}^- \text{H}^-$ ]; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = *iso*-propyl alcohol/ $\text{NH}_4\text{OH}/\text{H}_2\text{O}$  [7:1:2];  $R_f = 0.53$ ; Anal. Calcd for ( $\text{C}_{18}\text{H}_{23}\text{O}_5\text{PS} + 1 \text{ M H}_2\text{O} + 0.1 \text{ M EtOAc}$ ) C, 51.18; H, 6.15. Found: C, 51.01; H, 5.94.

### Example 45

**Compound 45:** [4,6-Dimethyl-5-(4'-hydroxy-3'-*iso*-propyl)benzyl]benzofuran-2-phosphonic Acid



Step a:

[0872] To a mixture of 3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenol (1.0 g, 3.18 mmol, Chiellini *et al.*, *Bioorg. Med. Chem. Lett.* 10:2607 (2000)) in  $\text{C}_2\text{H}_5\text{OH}$  (30.0 mL) and 40% aqueous methylamine (6.20 mL) at  $0^\circ\text{C}$  was added a solution of potassium iodide (2.5 g, 15.0 mmol) and iodine (0.98 g, 3.82 mmol) in  $\text{H}_2\text{O}$  (6.20 mL). The reaction mixture was stirred at  $0^\circ\text{C}$  for 1 h, quenched with water and extracted with ethyl acetate (2x30 mL). The organic layers were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with 20% ethyl acetate in

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hexanes to afford 3,5-dimethyl-2-iodo-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenol as white solid:  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  6.93 (m, 2 H), 6.65 (m, 2 H), 5.18 (s, 2 H), 4.05 (s, 2 H), 3.48 (s, 3 H), 3.30 (m, 1 H), 2.41 (s, 3 H), 2.19 (s, 3 H), 1.18 (d,  $J = 6.6$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:5);  $R_f = 0.60$ .

## Step b:

[0873] To a mixture of  $\text{Cu}_2\text{O}$  (0.08 g, 0.57 mmol) in DMF (2.0 mL) was added a solution of diethyl ethynylphosphonate (0.11g, 0.68 mmol) in DMF (0.5 mL) followed by a solution of 3,5-dimethyl-2-iodo-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenol in diisopropylethylamine (0.40 mL) and DMF (1.0 mL). The reaction mixture was heated at 90 °C for 48 h, cooled to room temperature and filtered through a Celite plug. The solution was diluted with water (30 mL) and extracted with ethyl acetate (30 mL). The organic layer was separated, dried over  $\text{MgSO}_4$ . The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel, eluting with 50% ethyl acetate in hexanes to afford diethyl [4,6-Dimethyl-5-(4'-hydroxy-3'-*iso*-propyl)benzyl]benzofuran-2-phosphonate (0.07 g, 26%) as colorless oil:  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.66 (dd,  $J = 8.1, 2.4$  Hz, 1 H), 7.35 (s, 1 H), 6.97 (d,  $J = 2.1$  Hz, 1 H), 6.92 (d,  $J = 8.1$  Hz, 1 H), 6.64 (dd,  $J = 8.1, 2.1$  Hz, 1 H), 5.18 (s, 2 H), 4.24 (m, 4 H), 4.14 (s, 2 H), 3.47 (s, 3 H), 3.30 (m, 1 H), 2.49 (s, 3 H), 2.39 (s, 3 H), 1.40 (t,  $J = 6.0$  Hz, 6 H), 1.14 (d,  $J = 6.6$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:1);  $R_f = 0.50$ .

## Step c:

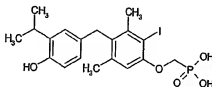
[0874] [4,6-Dimethyl-5-(4'-hydroxy-3'-*iso*-propyl)benzyl]benzofuran-2-phosphonic acid was prepared from diethyl [4,6-Dimethyl-5-(4'-hydroxy-3'-*iso*-propyl)benzyl]benzofuran-2-phosphonate according to the procedure described in example 7, step b: mp: 180-182 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.44 (dd,  $J = 8.1, 2.4$  Hz, 1 H), 7.30 (s, 1 H), 6.85 (d,  $J = 2.1$  Hz, 1

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H), 6.61 (d,  $J = 8.1$  Hz, 1 H), 6.55 (d,  $J = 8.1$  Hz, 1 H), 4.08 (s, 2 H), 3.24 (m, 1 H), 2.46 (s, 3 H), 2.37 (s, 3 H), 1.14 (d,  $J = 6.6$  Hz, 6 H); LC-MS  $m/z = 375$  [ $C_{20}H_{23}O_3P + H$ ] $^+$ ; Anal. Calcd for ( $C_{20}H_{23}O_3P + 0.7 H_2O + 0.1 CH_3OH$ ): C, 61.87; H, 6.41. Found: C, 61.80; H, 6.60.

### Example 46

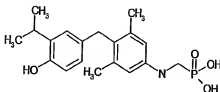
**Compound 46:** [3,5-Dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)-2-iodophenoxy]methylphosphonic Acid



[0875] The title compound was prepared from 3,5- dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxy)benzyl-2-iodophenol (compound 45,stepa) according to the procedure described in example 7:  $^1H$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  9.00 (s, 1 H), 6.87 (d,  $J = 3.9$  Hz, 1 H), 6.61 (d,  $J = 12.0$  Hz, 1 H), 6.40 (d,  $J = 12.6$  Hz, 1 H), 4.32 (d,  $J = 10.2$  Hz, 2 H), 3.94 (s, 2 H), 3.12 (m, 1 H), 2.36 (s, 3 H), 2.21 (s, 3 H); LC-MS  $m/z = 491$  [ $C_{19}H_{24}IO_5P + H$ ] $^+$ ; Anal Calcd for  $C_{19}H_{24}IO_5P$ : C, 46.55; H, 4.93. Found: C, 46.93; H, 4.99.

### Example 47

**Compound 47:** [3,5-Dimethyl 4-(4'-hydroxy-3'-*iso*-propylbenzyl)-phenylamino]methylphosphonic Acid



Step a:

[0876] A solution of 3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)-trifluoromethanesulfonyloxyphenyl (2.04 g, 4.57 mmol,

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intermediate for the synthesis of compound 24-1), triethylamine (1.27 mL, 9.14 mmol), 1,3-bis(diphenylphosphino)propane (0.19 mL, 0.45 mmol), MeOH (3.71 mL, 91.40 mmol), and Pd(OAc)<sub>2</sub> (0.102 g, 0.46 mmol) in DMF (25 mL) was heated at 90 °C under 60 psi of CO in a Parr reactor for 16 h. The reaction mixture was cooled to 0 °C, diluted with ethyl acetate (25 mL) and washed with H<sub>2</sub>O (25 mLx2). The organic solution was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:4) to afford methyl 3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)benzoate as an oil (1.52 g, 93%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.68 (s, 2 H), 6.97 (m, 1 H), 6.91 (m, 2 H), 6.20 (m, 1 H), 5.16 (s, 2 H), 4.01 (s, 3 H), 3.85 (s, 3 H), 3.21 (m, 1 H), 2.28 (s, 6 H), 1.14 (d, *J* = 6.0 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:4); R<sub>f</sub> = 0.42.

## Step b:

[0877] To a stirring solution of methyl 3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)benzoate (0.750 g, 2.11 mmol) in MeOH (20.0 mL) at 0 °C was added 1 M NaOH (12.64 mL, 12.64 mmol). The reaction mixture was heated at 50 °C for 16 h, cooled to 0 °C and acidified with 2 N HCl. The mixture was extracted with ethyl acetate (20 mL) and washed with H<sub>2</sub>O (10 mLx2). The solvent was removed under reduced pressure to afford 3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)benzoic acid as white solid (0.71 g, 98%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 12.76 (s, 1 H), 7.65 (s, 2 H), 6.98 (m, 1 H), 6.91 (m, 1 H), 6.60 (m, 1 H), 5.17 (s, 2H), 4.00 (s, 2 H), 3.37 (s, 3 H), 3.23 (m, 1 H), 2.27 (s, 6 H), 1.14 (d, *J* = 6.0 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (4:1); R<sub>f</sub> = 0.00.

## Step c:

[0878] To a suspension of 3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)benzoic acid (0.70 g, 2.04 mmol), *tert*-butanol (0.756 mg, 10.22

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mmol) and triethylamine (0.71 g, 5.11 mmol) in toluene (30 mL) was added diphenylphosphoryl azide (0.44 mL, 2.04 mmol). The reaction mixture was heated under reflux for 16 h, cooled to room temperature and poured into a cold solution of 0.25 M HCl (30 mL). The mixture was diluted with ethyl acetate and washed with H<sub>2</sub>O (30 mL). The organic layer was separated and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:9) to afford *t*-butyl *N*-3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)carbamate as a yellow oil (0.63 g, 75%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.16 (s, 1 H), 7.16 (s, 2 H), 6.96 (m, 1 H), 6.90 (m, 1 H), 6.62 (m, 1 H), 5.16 (s, 2 H), 3.86 (s, 2 H), 3.37 (s, 3 H), 3.22 (m, 1 H), 2.15 (s, 6 H), 1.48 (m, 9 H), 1.23 (d, *J* = 6.0 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (3:7); R<sub>f</sub> = 0.72.

Step d:

[0879] To a mixture of *t*-butyl *N*-3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)carbamate (0.315 g, 0.76 mmol) in THF (8.0 mL) at -78 °C was added lithium diisopropylamide (0.46 g, 0.91 mmol, 2.0 M solution in THF/heptane/ethylbenzene). The reaction mixture was stirred at -78 °C for 20 min and trifluoromethanesulfonic acid diethoxyphosphorylmethyl ester (0.16 g, 0.76 mmol) was added. The reaction mixture was stirred at -78 °C for 1 h, allowed to warm to room temperature and stirred for 4 h. The reaction mixture was quenched with 2.5 M aqueous ammonium chloride and diluted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride (8.0 mL), H<sub>2</sub>O (8.0 mL) and brine (8.0 mL). The organic solution was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:1) to afford diethyl *N*-*t*-butoxycarbonyl-[3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenylamino]methyl phosphonate as an oil (0.21 g, 49%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.00 (s, 2 H), 6.94 (m, 1 H), 6.90 (m, 1 H), 6.64 (m, 1 H), 5.16 (s, 2 H), 4.09 (d, *J* = 6.0 Hz, 2 H), 4.00 (m, 4 H), 3.8 (m, 2 H), 3.37 (s, 3 H), 3.22 (m, 1 H), 2.20 (s,

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6 H), 1.40 (s, 9 H), 1.27 (m, 6 H), 1.13 (m, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (3:2);  $R_f$  = 0.20

Step e:

[0880] To a stirring solution of diethyl *N*-*t*-butoxycarbonyl-[3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenylamino]methylphosphonate (0.19 g, 0.34 mmol) in MeOH (4.0 mL) at 0 °C was added 2 M HCl (1.68 mL, 3.37 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 48 h. The reaction mixture was cooled to 0 °C, neutralized with NaHCO<sub>3</sub>, diluted with ethyl acetate (20 mL) and washed with H<sub>2</sub>O (10 mLx2). The organic solution was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (3:2) to afford diethyl [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenylamino]methylphosphonate as a white solid (0.07 g, 51%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.95 (s, 1 H), 6.84 (m, 1 H), 6.63 (m, 1 H), 6.50 (m, 1 H), 6.45 (s, 2 H), 5.39 (m, 1H), 4.06 (s, 6 H), 3.74 (s, 2 H), 3.51 (m, 2 H), 3.13 (m, 1 H), 2.09 (s, 6 H), 1.20 (m, 6 H), 1.11 (d, *J* = 6.0 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (4:1);  $R_f$  = 0.29.

Step f:

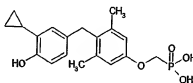
[0881] To a solution of diethyl [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenylamino]methylphosphonate (0.070 g, 0.17 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) at -30 °C was added bromotrimethylsilane (0.28 mL, 2.08 mmol). The reaction mixture was stirred at room temperature for 16 h and the solvent was removed under reduced pressure. The residue was treated with acetonitrile-water (4:1, 5.0 mL) and stirred at 38 °C for 30 min. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with H<sub>2</sub>O. The organic solution was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to afford the title compound as an off-white powder (0.050 g, 79%); mp: 147-150 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.97 (s, 1 H), 6.86 (m, 1 H), 6.59 (m, 1 H), 6.49 (m, 1 H), 6.45

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(s, 2 H), 3.74 (s, 2 H), 3.20 (d,  $J = 12.0$  Hz, 2 H), 3.13 (m, 1 H), 2.10 (s, 6 H), 1.12 (d,  $J = 6.0$  Hz, 6 H); LC-MS  $m/z = 364$  [ $C_{19}H_{26}NO_4P - H$ ] $^+$ ; Anal. Calcd for ( $C_{19}H_{26}NO_4P + 1.0 H_2O + 0.2 HBr + 0.2 CH_3CO_2CH_2CH_3$ ): C, 57.28; H, 7.23; N, 3.37; Br, 3.85. Found: C, 57.60; H, 7.33; N, 3.12; Br, 3.48.

### Example 48

**Compound 48:** [4-(3'-cyclopropyl-4'-hydroxybenzyl)-3,5-dimethylphenoxy] methylphosphonic acid



Step a:

[0882] To a suspension of methyltriposponium bromide (4.81 g, 13.46 mmol) in THF (10.0 mL) at 0 °C was added n-butyllithium (4.30 g, 10.76 mmol, 2.5 M solution in hexane). The reaction mixture was stirred at 0 °C for 1 h and to it was added a solution of 5-(2,6-dimethyl-4-triisopropylsilyloxybenzyl)-2-methoxymethoxy-benzaldehyde (1.23 g, 2.69 mmol, intermediate for the synthesis of Example 35, step d) in THF (5.0 mL). The reaction mixture was stirred at room temperature for 2.5 h, cooled to 0 °C and quenched with saturated ammonium chloride (15.0 mL). The mixture was extracted with ethyl acetate (20 mL), washed with H<sub>2</sub>O (25 mLx2) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:50) to afford triisopropyl-[3,5-dimethyl-4-(4'-methoxymethoxy-3'-vinylbenzyl)phenoxy]silane as oil (1.19 g, 97%); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.12 (m, 1 H), 7.00-6.93 (m, 2 H), 6.80 (m, 1 H), 6.59 (s, 2 H), 5.62 (d,  $J = 18.0$  Hz, 1 H), 5.24 (d,  $J = 12.0$  Hz, 1 H), 5.19 (s, 2 H), 3.88 (s, 2 H), 3.37 (s, 3 H), 2.15 (s, 6 H), 1.37 (s, 1 H), 1.21 (m, 3 H), 1.08 (d,  $J = 4.5$  Hz, 18 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:5);  $R_f = 0.74$ .



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## Step b:

[0883] A mixture of copper powder (0.094 g, 1.48 mmol) and iodine (0.005 g, 0.016 mmol) in benzene (2.3 mL) was stirred at room temperature for 10 min. To it was added a solution of triisopropyl-[3,5-dimethyl-4-(4'-methoxymethoxy-3'-vinylbenzyl)phenoxy]silane (0.15 g, 0.33 mmol) in benzene (1.0 mL) followed by diiodomethane (0.053 mL, 0.66 mmol). The reaction mixture was heated at 70 °C for 144 h, cooled to room temperature and filtered through a Celite plug. The solvent was removed under reduced pressure to afford triisopropyl-[4-(3'-cyclopropyl-4'-methoxymethoxybenzyl)-3,5-dimethylphenoxy]silane as oil (0.14 g, 91%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 6.92 (m, 1 H), 6.67 (m, 1 H), 6.58 (s, 2 H), 6.43 (s, 1 H), 5.18 (s, 2 H), 3.82 (s, 2 H), 3.39 (s, 3 H), 2.14 (s, 6 H), 1.26 (m, 3 H), 1.08 (d, *J* = 4.5 Hz, 18 H), 0.87 (m, 2 H), 0.46 (m, 2 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:5); R<sub>f</sub> = 0.74.

## Step c:

[0884] To a mixture of triisopropyl-[3,5-dimethyl-4-(3'-cyclopropyl-4'-methoxymethoxybenzyl)phenoxy]silane (0.38 g, 0.81 mmol) in THF (10.0 mL) at 0 °C was added TBAF (1.22 mL, 0.81 mmol, 1.0 M in THF). The reaction mixture was stirred at room temperature for 1 h, diluted with diethyl ether (20 mL) and washed with H<sub>2</sub>O (20 mLx2). The organic solution was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:9) to afford 4-(3'-cyclopropyl-4'-methoxymethoxybenzyl)-3,5-dimethylphenol as an oil (0.18 g, 71%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.01 (s, 1 H), 6.90 (m, 1 H), 6.61 (m, 1 H), 6.58 (s, 1 H), 6.46 (s, 2 H), 5.17 (s, 2 H), 3.77 (s, 2 H), 3.39 (s, 3 H), 2.11 (s, 6 H), 0.87 (m, 2 H), 0.51 (m, 2 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:9); R<sub>f</sub> = 0.47.

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## Step d:

[0885] To a mixture of 4-(3'-cyclopropyl-4'-methoxymethoxybenzyl)-3,5-dimethylphenol (0.16 g, 0.53 mmol) and  $\text{Cs}_2\text{CO}_3$  (0.859 g, 2.64 mmol) in DMF (6.0 mL) at 0 °C was added trifluoromethanesulfonic acid diethoxyphosphorylmethyl ester (0.11 g, 0.53 mmol). The reaction mixture was stirred at 0 °C for 5 h, allowed to warm to room temperature and stirred for 16 h. The reaction mixture was cooled to 0 °C, quenched with cold 1 N HCl and extracted with ethyl acetate (8.0 mL). The organic solution was dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:1) to afford diethyl [4-(3'-cyclopropyl-4'-methoxymethoxybenzyl)-3,5-dimethylphenoxy]methylphosphonate as oil (0.10 g, 28%);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  6.90 (m, 1 H), 6.75 (s, 2 H), 6.59 (m, 2 H), 5.17 (s, 2 H), 4.39 (d,  $J = 9.0$  Hz, 2 H), 4.15 (m, 4 H), 3.83 (s, 2 H), 3.39 (s, 3 H), 2.19 (s, 6 H), 2.09 (m, 1 H), 1.24 (m, 6 H), 0.87 (m, 2 H), 0.52 (m, 2 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (4:1);  $R_f = 0.25$

## Step e:

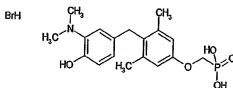
[0886] To a solution of diethyl [4-(3'-cyclopropyl-4'-methoxymethoxybenzyl)-3,5-dimethylphenoxy]methylphosphonate (0.090 g, 0.19 mmol) in  $\text{CH}_2\text{Cl}_2$  (3.0 mL) at -30 °C was added bromotrimethylsilane (0.26 mL, 1.94 mmol). The reaction mixture was stirred at room temperature 16 h and the solvent was removed under reduced pressure. The residue was treated with acetonitrile-water (4:1, 5.0 mL), stirred at 38 °C for 30 min and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with  $\text{H}_2\text{O}$ . The organic solution was dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to afford the title compound as an off-white powder (0.040 g, 57%); mp: 153-156 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.02 (s, 1 H), 6.67 (s, 2 H), 6.58 (m, 1 H), 6.41 (m, 2 H), 4.00 (d,  $J = 10.5$  Hz, 2 H), 3.75 (s, 2 H), 2.13 (s, 6 H), 1.98 (m, 1 H), 0.81 (m, 2 H),

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0.47 (m, 2 H); LC-MS  $m/z$  = 362  $[\text{C}_{19}\text{H}_{23}\text{O}_5\text{P} - \text{H}]^+$ ; Anal. Calcd for  $(\text{C}_{19}\text{H}_{23}\text{O}_5\text{P} + 0.9 \text{ H}_2\text{O})$ : C, 60.28; H, 6.60. Found: C, 60.40; H, 6.92.

### Example 49

**Compound 49:** [4-(3'-Dimethylamino-4'-hydroxybenzyl)-3,5-dimethylphenoxy]methylphosphonic acid



Step a:

[0887] To a stirring solution of 4-bromo-2-nitro-phenol (6 g, 27.52 mmol) in MeOH (150 mL) at room temperature was added a suspension of  $\text{Na}_2\text{S}_2\text{O}_4$  (29 g, 165.13 mmol). The mixture was stirred at room temperature for 3 hrs, filtered and concentrated down. The residue was partitioned between EtOAc and water. The organic layer was collected and dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to afford crude 2-amino-4-bromo-phenol as a yellow solid (3.9 g, 75%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.27 (s, 1 H), 6.70 (d,  $J$  = 2.2 Hz, 1 H), 6.50 (m, 2 H), 4.79 (s, 2 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 20% ethyl acetate in hexanes;  $R_f$  = 0.35.

Step b:

[0888] 2-Amino-4-bromo-phenol (3.9 g, 20.74 mmol) was dissolved into AcOH (120 mL) and heated to 40 °C. To this stirring solution at 40 °C was added  $(\text{HCHO})_n$  (1.9 g, 62.23 mmol), followed by  $\text{NaBH}_3\text{CN}$  (3.9 g, 62.23 mmol). The reaction mixture was stirred for 1 hr at 40 °C, then another  $(\text{HCHO})_n$  (1.9 g, 62.23 mmol) and  $\text{NaBH}_3\text{CN}$  (3.9 g, 62.23 mmol) were added. The mixture was stirred for 16 hrs at 40 °C. The solvent was removed under reduced pressure. The residues were partitioned between EtOAc and water. The organic layer was collected and dried over  $\text{Na}_2\text{SO}_4$ , filtered and

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concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (30:70) to afford 4-bromo-2-dimethylamino-phenol as a light yellow solid (3.7 g, 83%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.44 (s, 1 H), 6.92 (m, 2 H), 6.71 (d,  $J = 8.4$  Hz, 1 H), 2.69 (s, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 20% ethyl acetate in hexanes;  $R_f = 0.57$ .

Step c:

[0889] To a stirring solution of 4-bromo-2-dimethylamino-phenol (3.7 g, 17.13 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) at room temperature was added ethyl-diisopropyl-amine (4.47 mL, 25.7 mmol) and chloro-methoxy-methane (1.69 mL, 22.27 mmol). The mixture was refluxed for 16 hrs, added water. The organic layer was collected and dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to afford crude *N*-(5-bromo-2-methoxymethoxyphenyl)dimethylamine as a red oil (4.4 g, 99%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ): 6.96 (m, 3 H), 5.17 (s, 2 H), 3.40 (s, 3 H), 2.72 (s, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 15% ethyl acetate in hexanes;  $R_f = 0.59$ .

Step d:

[0890] To a stirring solution of *N*-(5-bromo-2-methoxymethoxy-phenyl)dimethylamine (3.4 g, 13.07 mmol) in THF (80 mL) at  $-78^\circ\text{C}$  was added *n*-BuLi (5.22 mL, 2.5 M in hexanes). The mixture was stirred at  $-78^\circ\text{C}$  for 1 hr and a solution of 2,6-dimethyl-4-triisopropylsilyloxy-benzaldehyde (3.6 g, 11.77 mmol) was added. The reaction mixture was stirred at  $-78^\circ\text{C}$  for 1 hr, allowed to warm to room temperature and stirred for 1 hr. The reaction mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  and diluted with diethyl ether. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (30:70) to afford (3-dimethylamino-4-methoxymethoxy-phenyl)-(2,6-dimethyl-4-triisopropylsilyloxyphenyl)methanol as a yellow oil (4 g, 63%):  $^1\text{H}$  NMR (300 MHz,

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DMSO-*d*<sub>6</sub>):  $\delta$  6.89 (d,  $J$  = 8.4 Hz, 1 H), 6.79 (s, 1 H), 6.61 (m, 1 H), 6.51 (s, 2 H), 6.01 (d,  $J$  = 4.0 Hz, 1 H), 5.65 (d,  $J$  = 4.0 Hz, 1 H), 5.14 (s, 2 H), 3.41 (s, 3 H), 2.64 (s, 6 H), 2.17 (s, 6 H), 1.24 (m, 3 H), 1.08 (d,  $J$  = 7.2 Hz, 18 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 25% ethyl acetate in hexanes;  $R_f$  = 0.27.

Step e:

[0891] To a stirring solution of (3-dimethylamino-4-methoxymethoxy-phenyl)-(2,6-dimethyl-4-triisopropylsilyloxy-phenyl)-methanol (3.4 g, 6.97 mmol) in  $\text{CH}_2\text{Cl}_2$  (150 mL) at room temperature was added  $\text{Et}_3\text{SiH}$  (5.6 mL, 34.85 mmol) and TFA (2.6 mL, 34.85 mmol). The reaction mixture was stirred at room temperature for 6 hrs. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and saturated  $\text{NaHCO}_3$ . The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (3:7) to afford *N*-[5-(2',6'-dimethyl-4'-triisopropylsilyloxybenzyl)-2-methoxymethoxyphenyl]dimethylamine as a yellow oil (3 g, 91%);  $^1\text{H}$  NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  6.86 (d,  $J$  = 8.1 Hz, 1 H), 6.59 (s, 2 H), 6.54 (d,  $J$  = 2.1 Hz, 1 H), 6.41 (m, 1 H), 5.12 (s, 2 H), 3.85 (s, 2 H), 3.40 (s, 3 H), 2.64 (s, 6 H), 2.15 (s, 6 H), 1.26 (m, 3 H), 1.08 (d,  $J$  = 7.2 Hz, 18 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (25:75);  $R_f$  = 0.54.

Step f:

[0892] To a stirring solution of *N*-[5-(2',6'-dimethyl-4'-triisopropylsilyloxybenzyl)-2-methoxymethoxyphenyl]dimethylamine (3 g, 6.36 mmol) in THF (60 mL) at room temperature was added tetrabutylammonium fluoride (9.54 mL, 1.0 M in THF). The reaction mixture was stirred at room temperature for 2 hr, diluted with diethyl ether and washed with water (30 mLx2). The solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting

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with ethyl acetate-hexanes (1:1) to afford 4-(3'-dimethylamino-4'-methoxymethoxybenzyl)-3,5-dimethylphenol as a light yellow oil (1.8 g, 90%):  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  9.01 (s, 1 H),  $\delta$  6.85 (d,  $J$  = 8.1 Hz, 1 H), 6.63 (d,  $J$  = 2.1 Hz, 1 H), 6.47 (s, 2 H), 6.35 (m, 1 H), 5.12 (s, 2 H), 3.80 (s, 2 H), 3.40 (s, 3 H), 2.67 (s, 6 H), 2.17 (s, 6 H), TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 30% ethyl acetate in hexanes;  $R_f$  = 0.28.

## Step g:

[0893] To a stirring solution of 4-(3'-dimethylamino-4'-methoxymethoxybenzyl)-3,5-dimethylphenol (0.525 g, 1.66 mmol) in DMF (18 mL) at 0 °C was added NaH (80 mg, 1.99 mmol, 60%) and stirred for 1 hr at room temperature. Diethyl tosyloxymethylphosphonate (0.7 g, 2.16 mmol) was added and the mixture was stirred for 16 hrs at room temperature. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and sat.  $\text{NaHCO}_3$ . The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (8:2) to afford diethyl [4-(3'-dimethylamino-4'-methoxymethoxybenzyl)-3,5-dimethylphenoxy]methylphosphonate as a light yellow oil (0.5 g, 65%):  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  6.85 (d,  $J$  = 8.1 Hz, 1 H), 6.76 (s, 2 H), 6.64 (d,  $J$  = 2.1 Hz, 1 H), 6.34 (m, 1 H), 5.12 (s, 2 H), 4.38 (d,  $J$  = 9.8 Hz, 2 H), 4.14 (m, 4 H), 3.86 (s, 2 H), 3.40 (s, 3 H), 2.67 (s, 6 H), 2.19 (s, 6 H), 1.25 (t,  $J$  = 7.0 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (6:4);  $R_f$  = 0.43.

## Step h:

[0894] To a stirring solution of diethyl [4-(3'-dimethylamino-4'-methoxymethoxybenzyl)-3,5-dimethylphenoxy]methylphosphonate (0.48 g, 1.03 mmol) in MeOH (6 mL) and water (1 mL) at room temperature was added HCl (1.03 mL, 10 N), and heated at 100 °C for 5 min by microwave. The solvent was removed under reduced pressure, and the residue was

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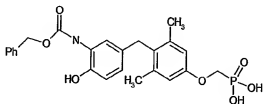
partitioned between EtOAc and sat.  $\text{NaHCO}_3$ . The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-  $\text{CH}_2\text{Cl}_2$  (3:1) to afford diethyl [4-(3'-dimethylamino-4'-hydroxybenzyl)-3,5-dimethyl-phenoxy]methylphosphonate as a light yellow oil (0.29 g, 67%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.77 (s, 1 H),  $\delta$  6.72 (s, 2 H), 6.57 (m, 2 H), 6.26 (m, 1 H), 4.35 (d,  $J = 9.8$  Hz, 2 H), 4.13 (m, 4 H), 3.79 (s, 2 H), 2.60 (s, 6 H), 2.17 (s, 6 H), 1.25 (t,  $J = 7.0$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate- $\text{CH}_2\text{Cl}_2$  (1:3);  $R_f = 0.49$ .

Step i:

[0895] The title compound was prepared according to the procedure described for the synthesis of compound 8, step f.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.34 (s, 1 H), 6.92 (d,  $J = 8.7$  Hz, 1 H), 6.79 (m, 1 H), 6.73 (s, 2 H), 4.03 (d,  $J = 10.2$  Hz, 2 H), 3.88 (s, 2 H), 3.13 (s, 6 H), 2.17 (s, 6 H); mp: degasses at  $90^\circ\text{C}$ ; LC-MS  $m/z = 366$  [ $\text{C}_{18}\text{H}_{24}\text{NO}_5\text{P} + \text{H}$ ] $^+$ ; Anal Calcd for ( $\text{C}_{18}\text{H}_{24}\text{NO}_5\text{P} + 1.4\text{HBr} + 0.4\text{H}_2\text{O} + 0.1\text{MeOH}$ ): C, 44.45; H, 5.48; N, 2.86; Br, 22.87. Found: C, 44.64; H, 5.67; N, 2.65; Br, 22.74.

### Example 50

**Compound 50:** [4-(3'-Benzyloxycarbonylamino-4'-hydroxybenzyl)-3,5-dimethyl-phenoxy]methylphosphonic acid



Step a:

[0896] To a stirring solution of diethyl [3,5-dimethyl-4-(3'-carboxyl-4'-methoxymethoxybenzyl)phenoxy]methylphosphonate (0.36 g, 0.77 mmol) in

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toluene (20 mL) at room temperature was added diphenylphosphoryl azide (0.17 mL, 0.77 mmol), triethylamine (0.2 mL, 1.4 mmol) and benzyl alcohol (0.4 mL, 3.85 mmol). The mixture was refluxed for 16 hrs. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and sat.  $\text{NH}_4\text{Cl}$ . The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate to afford diethyl [4-(3'-benzyloxycarbonylamino-4'-methoxymethoxybenzyl)-3,5-dimethylphenoxy]methylphosphonate as a light yellow oil (0.4 g, 91%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.60 (s, 1 H), 7.38 (m, 6 H), 6.99 (d,  $J = 8.4$  Hz, 1 H), 6.76 (s, 2 H), 6.65 (m, 1 H), 5.13 (s, 2 H), 5.12 (s, 2 H), 4.37 (d,  $J = 9.6$  Hz, 2 H), 4.13 (m, 4 H), 3.87 (s, 2 H), 3.37 (s, 3 H), 2.19 (s, 6 H), 1.27 (t,  $J = 6.9$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 75% ethyl acetate in hexanes;  $R_f = 0.45$ .

Step b:

[0897] To a stirring solution of diethyl [4-(3'-benzyloxycarbonylamino-4'-methoxymethoxybenzyl)-3,5-dimethylphenoxy]methylphosphonic (0.1 g, 0.175 mmol) in MeOH (2 mL) at room temperature was added HCl (0.18 mL, 10 N), and the reaction mixture was heated at 100 °C for 5 min by microwave. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and sat.  $\text{NaHCO}_3$ . The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate to afford diethyl [4-(3'-benzyloxycarbonylamino-4'-hydroxybenzyl)-3,5-dimethylphenoxy]methylphosphonate as a light yellow oil (0.076 g, 82%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.48 (s, 1 H), 8.34 (s, 1 H), 7.38 (m, 6 H), 6.71 (m, 3 H), 6.53 (m, 1 H), 5.11 (s, 2 H), 4.37 (d,  $J = 9.6$  Hz, 2 H), 4.13 (m, 4 H), 3.82 (s, 2 H), 2.19 (s, 6 H), 1.27 (t,  $J = 6.9$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 75% ethyl acetate in hexanes;  $R_f = 0.40$ .



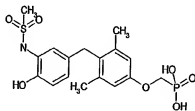
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Step c:

[0898] To a stirring solution of diethyl [4-(3'-benzyloxycarbonylamino-4'-hydroxybenzyl)-3,5-dimethylphenoxy]methylphosphonic (0.076 g, 0.144 mmol) in  $\text{CH}_2\text{Cl}_2$  (8 mL) at room temperature was added hexamethyldisilazane (0.28 mL, 1.27 mmol) and bromotrimethylsilane (0.15 mL, 1.15 mmol). The reaction mixture was stirred at room temperature for 16 hrs. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and water. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was washed by  $\text{CH}_2\text{Cl}_2$  to afford the title compound as a white amorphous solid (0.03 g, 44%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.41 (s, 1 H), 8.30 (s, 1 H), 7.33 (m, 6 H), 6.66 (m, 3 H), 6.48 (m, 1 H), 5.08 (s, 2 H), 3.97 (d,  $J = 10.2$  Hz, 2 H), 3.77 (s, 2 H), 2.13 (s, 6 H). mp: shrink at 180 °C. LC-MS  $m/z = 472$  [ $\text{C}_{24}\text{H}_{26}\text{NO}_7\text{P} + \text{H}$ ] $^+$ ; Anal Calcd for ( $\text{C}_{24}\text{H}_{26}\text{NO}_7\text{P} + 1.1\text{H}_2\text{O}$ ): C, 58.68; H, 5.79; N, 2.85. Found: C, 58.44; H, 5.89; N, 2.77.

## Example 51:

**Compound 51-1:** [3,5-dimethyl-4-(4'-Hydroxy-3'-methanesulfonylamino-benzyl)phenoxy]methylphosphonic acid



Step a:

[0899] To a solution of diethyl [4-(3'-benzyloxycarbonylamino-4'-methoxymethoxybenzyl)-3,5-dimethylphenoxy]methylphosphonic (0.33 g, 0.58 mmol) in EtOH (20 mL) at room temperature was added Pd/C (50 mg). The reaction mixture was stirred at room temperature under 50 psi  $\text{H}_2$  for 16 hrs then filtered through Celite®. The solvent was removed under reduced

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pressure to afford diethyl [4-(3'-amino-4'-methoxymethoxybenzyl)-3,5-dimethylphenoxy]methylphosphonate as a colorless oil (0.25 g, 99%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  6.76 (m, 3 H), 6.29 (d,  $J = 2.4$  Hz, 1 H), 6.12 (m, 1 H), 5.07 (s, 2 H), 4.69 (s, 2 H), 4.35 (d,  $J = 10.2$  Hz, 2 H), 4.12 (m, 4 H), 3.76 (s, 2 H), 3.39 (s, 3 H), 2.19 (s, 6 H), 1.27 (t,  $J = 7$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 75% ethyl acetate in hexanes;  $R_f = 0.51$ .

## Step b:

[0900] To a stirring solution of diethyl [4-(3'-amino-4'-methoxymethoxybenzyl)-3,5-dimethylphenoxy]methylphosphonic (0.13 g, 0.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at room temperature was added pyridine (0.037 mL, 0.45 mmol) and methanesulfonyl chloride (0.026 mL, 0.33 mmol). The reaction mixture was stirred at room temperature for 16 hrs. then partitioned between  $\text{CH}_2\text{Cl}_2$  and water. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate to afford diethyl [3,5-dimethyl-4-(3'-methanesulfonylamino-4'-methoxymethoxybenzyl)phenoxy]methylphosphonate as a light yellow oil (0.12 g, 77%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.91 (s, 1 H), 7.02 (d,  $J = 8.4$  Hz, 1 H), 6.96 (d,  $J = 2.1$  Hz, 1 H), 6.76 (m, 3 H), 5.18 (s, 2 H), 4.37 (d,  $J = 9.9$  Hz, 2 H), 4.16 (m, 4 H), 3.87 (s, 2 H), 3.41 (s, 3 H), 2.93 (s, 3 H), 2.19 (s, 6 H), 1.27 (t,  $J = 6.9$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 75% ethyl acetate in hexanes;  $R_f = 0.42$ .

## Step c:

[0901] To a stirring solution of diethyl[3,5-dimethyl-4-(3'-methanesulfonylamino-4'-methoxymethoxybenzyl)phenoxy]methyl phosphonate (0.12 g, 0.23 mmol) in MeOH (2 mL) at room temperature was added HCl (1.2 mL, 2 N), and the reaction mixture was heated at 100 °C for 5 min by microwave. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and sat.  $\text{NaHCO}_3$ . The organic layer

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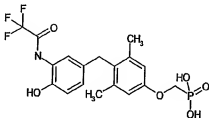
was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate to afford diethyl[3,5-dimethyl-4-(4'-hydroxy-3'-methanesulfonylaminobenzyl)phenoxy]methylphosphonate as a white solid (0.08g, 74%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  6.85 (d,  $J = 1.8$  Hz, 1 H), 6.76 (m, 3 H), 6.63 (m, 1 H), 4.37 (d,  $J = 9.9$  Hz, 2 H), 4.14 (m, 4 H), 3.82 (s, 2 H), 2.89 (s, 3 H), 2.18 (s, 6 H), 1.27 (t,  $J = 6.9$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate;  $R_f = 0.42$ .

Step d:

[0902] The title compound was prepared according to the procedure described in example 8, step f, (60 mg, 85%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.61 (s, 1 H), 8.61 (s, 1 H), 6.74 (m, 5 H), 4.02 (d,  $J = 10.2$  Hz, 2 H), 3.80 (s, 2 H), 2.88 (s, 3 H), 2.16 (s, 6 H); mp: shrinks at  $200^\circ\text{C}$ ; LC-MS  $m/z = 416$  [ $\text{C}_{17}\text{H}_{22}\text{NO}_7\text{PS} + \text{HJ}^+$ ]; Anal Calcd for ( $\text{C}_{17}\text{H}_{22}\text{NO}_7\text{PS} + 0.1\text{MeOH} + 0.8\text{H}_2\text{O}$ ): C, 47.43; H, 5.59; N, 3.23. Found: C, 47.57; H, 5.68; N, 3.10.

[0903] Using the appropriate starting materials, compounds 51-2 was prepared in an analogous manner to that described for the synthesis of compound 51-1

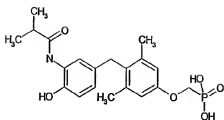
**Compound 51-2:** [3,5-Dimethyl-4-(4'-hydroxy-3'-trifluoroacetylaminobenzyl)phenoxy]methylphosphonic acid



[0904]  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  10.41 (s, 1 H), 9.71 (s, 1 H), 6.95 (s, 1 H), 6.74 (m, 4 H), 4.03 (d,  $J = 10.2$  Hz, 2 H), 3.83 (s, 2 H), 2.16 (s, 6 H); mp:  $170 - 172^\circ\text{C}$ ; LC-MS  $m/z = 434$  [ $\text{C}_{18}\text{H}_{19}\text{F}_3\text{NO}_6\text{P} + \text{HJ}^+$ ]; Anal Calcd for ( $\text{C}_{18}\text{H}_{19}\text{F}_3\text{NO}_6\text{P} + 0.4\text{H}_2\text{O}$ ): C, 49.08; H, 4.53; N, 3.18. Found: C, 49.26; H, 4.75; N, 2.83.

**Compound 51-3:** [3,5-dimethyl-4-(4'-Hydroxy-3'-isobutrylaminobenzyl)phenoxy]methylphosphonic acid

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Step a:

[0905] Diethyl (3'-amino-4'-hydroxybenzyl)-3,5-dimethylphenoxy]methylphosphonate was prepared according to the procedure described for the synthesis of example 51-1, step c:  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.70 (s, 1 H), 6.71 (s, 2 H), 6.48 (d,  $J = 7.6$  Hz, 1 H), 6.19 (s, 1 H), 6.01 (m, 1 H), 4.38 (s, 2 H), 4.33 (d,  $J = 9.6$  Hz, 2 H), 4.12 (m, 4 H), 3.70 (s, 2 H), 2.16 (s, 6 H), 1.23 (t,  $J = 7.4$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 75% ethyl acetate in hexanes;  $R_f = 0.46$ .

Step b:

[0906] To a stirring solution of diethyl (3'-amino-4'-hydroxybenzyl)-3,5-dimethylphenoxy]methylphosphonate (0.046 g, 0.12 mmol) in THF (5 mL) at 0 °C was added pyridine (0.015 mL, 0.18 mmol) and isobutyric anhydride (0.021 mL, 0.13 mmol). The reaction mixture was stirred at 50 °C for 16 hrs. It was added EtOAc and water. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate to afford diethyl [3,5-dimethyl-4-(4'-hydroxy-3'-isobutyrylamino)benzyl]phenoxy]methylphosphonate as a yellow oil (0.046 g, 83%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.55 (s, 1 H), 9.22 (s, 1 H), 7.36 (s, 1 H), 6.73 (m, 3 H), 6.58 (m, 1 H), 4.36 (d,  $J = 9.6$  Hz, 2 H), 4.13 (m, 4 H), 3.82 (s, 2 H), 2.73 (m, 1 H), 2.19 (s, 6 H), 1.27 (t,  $J = 6.9$  Hz, 6 H), 1.07 (d,  $J = 6.9$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 80% ethyl acetate in hexanes;  $R_f = 0.37$ .

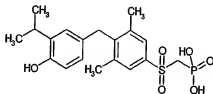
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Step c:

[0907] The title compound was prepared according to the procedure described for the synthesis of example 8, step f:  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.51 (s, 1 H), 9.22 (s, 1 H), 7.33 (s, 1 H), 6.72 (m, 3 H), 6.58 (m, 1 H), 4.03 (d,  $J = 10.2$  Hz, 2 H), 3.80 (s, 2 H), 2.71 (m, 1 H), 2.17 (s, 6 H), 1.06 (d,  $J = 7.0$  Hz, 6 H); LC-MS  $m/z = 408$  [ $\text{C}_{20}\text{H}_{26}\text{NO}_6\text{P} + \text{H}$ ] $^+$ ; Anal Calcd for ( $\text{C}_{20}\text{H}_{26}\text{NO}_6\text{P} + 0.9\text{H}_2\text{O} + 0.45\text{HBr}$ ): C, 52.22; H, 6.19; N, 3.04; Br, 7.82. Found: C, 52.31; H, 6.42; N, 2.66; Br, 7.60.

## Example 52:

**Compound 52:** [3,5-dimethyl-4-(4'-Hydroxy-3'-*iso*-propylbenzyl) benzenesulfonyl]methylphosphonic acid



Step a:

[0908] To a stirring solution of 3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenylamine (0.5 g, 1.6 mmol) at 80 °C in dimethyldisulfide (5 mL) was added isoamylnitrite (0.86 mL, 6.4 mmol). The reaction mixture was stirred at 80 °C for 1 h. The solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:3) to afford 3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)methylsulfanylbenzene as a light yellow oil (0.24 g, 44%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3-d_1$ ):  $\delta$  6.90 - 6.94 (m, 4 H), 6.62 (m, 1 H), 5.19 (s, 2 H), 3.97 (s, 2 H), 3.50 (s, 3 H), 3.31 (m, 1 H), 2.52 (s, 3 H), 2.25 (s, 6H) 1.20 (d,  $J = 6.9$  Hz, 6 H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:2);  $R_f = 0.73$ .

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Step b:

[0909] To a stirring solution of 3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)methylsulfonylbenzene (0.24 g, 0.7 mmol) at room temperature in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added *m*-CPBA (0.42 g, 2.45 mmol). The reaction mixture was stirred at room temperature for 16 hrs. It was quenched by sat.  $\text{Na}_2\text{SO}_3$ . The organic layer was washed by sat.  $\text{NaHCO}_3$  and dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to afford 3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)methylsulfonylbenzene as a light yellow oil (0.23 g, 87%):  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ - $d_1$ ):  $\delta$  7.62 (s, 2 H), 6.88 (m, 2 H), 6.55 (m, 1 H), 5.16 (s, 2 H), 4.10 (s, 2 H), 3.46 (s, 3 H), 3.28 (m, 1 H), 3.06 (s, 3 H), 2.33 (s, 6H) 1.17 (d,  $J$  = 6.9 Hz, 6 H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:2);  $R_f$  = 0.46.

Step c:

[0910] To a stirring solution of 3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)methylsulfonylbenzene (0.23 mL, 0.61 mmol) in THF (10 mL) at  $-78^\circ\text{C}$  was added *n*-BuLi (2.5 M in hexanes, 0.29 mL), the reaction mixture was stirred at  $-78^\circ\text{C}$  for 1 hr and at  $0^\circ\text{C}$  for 40 min, then diethyl phosphorochloridate (0.11 mL, 0.73 mmol) was added at  $0^\circ\text{C}$ . The reaction mixture was stirred at room temperature for 1 hr. The reaction mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  and diluted with diethyl ether. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate to afford diethyl [3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenylsulfonyl]methylphosphonate as a light yellow oil (130 mg, 42%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.63 (s, 2 H), 7.00 (d,  $J$  = 3.0 Hz, 1 H), 6.88 (d,  $J$  = 8.4 Hz, 1 H), 6.60 (dd,  $J$  = 3.0, 8.4 Hz, 1 H), 5.15 (s, 2 H), 4.36 (d,  $J$  = 17.2 Hz, 2 H), 3.97 (m, 6 H), 3.36 (s, 3 H), 3.22 (m, 1 H), 2.31 (s, 6H), 1.19 (m, 12 H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (3:1);  $R_f$  = 0.43.

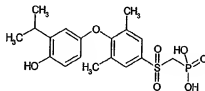
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Step d:

[0911] The title compound was prepared by the procedure described for the synthesis of example 8, step f:  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  9.08 (s, 1 H), 7.61 (s, 2 H), 6.89 (d,  $J = 3.0$  Hz, 1 H), 6.62 (d,  $J = 8.0$  Hz, 1 H), 6.43 (d,  $J = 3.0$ , 8.0 Hz, 1 H), 3.96 (s, 2 H), 3.85 (d,  $J = 16.6$  Hz, 2 H), 3.13 (m, 1 H), 2.28 (s, 6 H), 1.10 (d,  $J = 6.8$  Hz, 6 H); LC-MS  $m/z = 413$  [ $\text{C}_{19}\text{H}_{25}\text{O}_6\text{PS} + \text{H}$ ] $^+$ ; Anal Calcd for ( $\text{C}_{19}\text{H}_{25}\text{O}_6\text{PS} + 1.0\text{H}_2\text{O} + 0.15\text{HBr} + 0.2\text{Et}_2\text{O}$ ): C, 51.99; H, 6.42; Br, 2.62. Found: C, 51.67; H, 6.50; Br, 2.62.

### Example 53

**Compound 53:** [3,5-dimethyl-4-(4'-Hydroxy-3'-*iso*-propylphenoxy)benzenesulfonyl]methylphosphonic acid



Step a:

[0912] To a stirring solution of 4-bromo-2,6-dimethylphenol (6 g, 29.85 mmol) in  $\text{CH}_2\text{Cl}_2$  (80 mL) at  $0^\circ\text{C}$  was added imidazole (4.1 g, 59.70 mmol) and triisopropylsilyl chloride (7.1 mL, 32.84 mmol). The reaction mixture was stirred at room temperature for 16 hrs. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:9) to afford (4-bromo-2,6-dimethylphenoxy)triisopropylsilane as a colorless oil (1.6 g, 15%);  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  7.19 (s, 2 H), 2.20 (s, 6 H), 1.29 (m, 3 H), 1.10 (d,  $J = 7.2$  Hz, 18 H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (5:95);  $R_f = 0.70$ .

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## Step b:

[0913] To a stirring solution of (4-bromo-2,6-dimethylphenoxy)triisopropylsilane (0.5 g, 1.4 mmol) in THF (15 mL) at  $-78^{\circ}\text{C}$  was added *n*-BuLi (2.5 M in hexanes, 0.56 mL), the reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 1 hr, then dimethyldisulfide (0.16 mL, 1.82 mmol) was added at  $-78^{\circ}\text{C}$ . The reaction mixture was stirred at room temperature for 1 h and quenched with saturated  $\text{NH}_4\text{Cl}$  and diluted with diethyl ether. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to afford crude (2,6-dimethyl-4-methylsulfonylphenoxy)triisopropylsilane as an oil (0.46 g, 100%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  6.92 (s, 2 H), 2.41 (s, 3 H), 2.20 (s, 6 H), 1.29 (m, 3 H), 1.10 (d,  $J = 7.2$  Hz, 18 H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (2:98);  $R_f = 0.57$ .

## Step c:

[0914] To a stirring solution of (2,6-dimethyl-4-methylsulfonylphenoxy)triisopropylsilane (0.46 g, 1.4 mmol) in  $\text{CH}_2\text{Cl}_2$  (15 mL) at room temperature was added *m*-CPBA (0.85 g, 4.9 mmol). The reaction mixture was stirred at room temperature for 16 hrs. It was quenched by sat.  $\text{Na}_2\text{SO}_3$ . The organic layer was washed by sat.  $\text{NaHCO}_3$  and dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to afford crude (2,6-dimethyl-4-methanesulfonylphenoxy)triisopropylsilane as an oil (0.47 g, 94%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.57 (s, 2 H), 3.14 (s, 3 H), 2.28 (s, 6 H), 1.19 (m, 3 H), 1.10 (d,  $J = 7.2$  Hz, 18 H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (5:95);  $R_f = 0.49$ .

## Step d:

[0915] To a stirring solution of (2,6-dimethyl-4-methanesulfonylphenoxy)triisopropylsilane (0.47 g, 1.32 mmol) in THF (15 mL) at  $-78^{\circ}\text{C}$  was added *n*-BuLi (2.5 M in hexanes, 0.58 mL), the reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 1 hr, then diethyl phosphorochloridate (0.25 mL, 1.72 mmol) was added at  $-78^{\circ}\text{C}$ . The reaction mixture was stirred at



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room temperature for 16 hrs. The reaction mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  and diluted with diethyl ether. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:1) to afford diethyl (3,5-dimethyl-4-triisopropylsilyloxybenzenesulfonyl)methylphosphonate as a colorless oil (0.1 g, 15%):  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ - $d_6$ ):  $\delta$  7.57 (s, 2 H), 4.17 (m, 4 H), 3.71 (d,  $J$  = 17.2 Hz, 2 H), 2.29 (s, 6 H), 1.33 (m, 9 H), 1.10 (d,  $J$  = 7.2 Hz, 18 H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:1);  $R_f$  = 0.45.

## Step e:

- [0916] To a stirring solution diethyl (3,5-dimethyl-4-triisopropylsilyloxybenzenesulfonyl)methylphosphonate in THF (3 mL) at room temperature was added TBAF (0.3 mL, 1 M in THF). It was stirred at room temperature for 2 hrs. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (5:1) to afford diethyl (3,5-dimethyl-4-hydroxybenzenesulfonyl)methylphosphonate as a light yellow oil (70 mg, 100%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ - $d_6$ ):  $\delta$  7.54 (s, 2 H), 4.12 (m, 4 H), 3.65 (d,  $J$  = 16.8 Hz, 2 H), 2.22 (s, 6 H), 1.22 (d,  $J$  = 7.2 Hz, 6 H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (5:1);  $R_f$  = 0.44.

## Step f:

- [0917] To a stirring mixture of bis(4-methoxy-3-*iso*-propylphenyl)iodonium tetrafluoroborate (0.15 g, 0.3 mmol) and copper powder (16 mg, 0.26 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) at 0 °C was added a solution of triethylamine (0.031 mL, 0.22 mmol) and diethyl (3,5-dimethyl-4-hydroxybenzenesulfonyl)methylphosphonate (70 mg, 0.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL). The reaction

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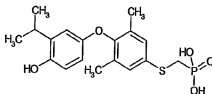
mixture was stirred at room temperature for 16 hrs and filtered through a Celite plug. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (5:1) to afford diethyl[3,5-dimethyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)benzenesulfonyl]methylphosphonate as a light yellow oil (40 mg, 41%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.76 (s, 2 H), 6.79 (m, 2 H), 6.35 (m, 1 H), 4.44 (d,  $J = 16.8$  Hz, 2 H), 4.02 (m, 4 H), 3.73 (s, 3 H), 3.18 (m, 1 H), 2.14 (s, 6 H), 1.15 (m, 12 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (3:2);  $R_f = 0.49$ .

Step g:

[0918] The title compound was prepared according to the procedure described for the synthesis of example 22, step d, (40 mg, 0.083 mmol):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.02 (s, 1 H), 7.70 (s, 2 H), 6.67 (m, 2 H), 6.19 (dd,  $J = 3.0, 8.4$  Hz, 1 H), 3.72 (d,  $J = 15.8$  Hz, 2 H), 3.14 (m, 1 H), 2.09 (s, 6 H), 1.11 (d,  $J = 6.6$  Hz, 6 H); LC-MS  $m/z = 415$  [ $\text{C}_{18}\text{H}_{23}\text{O}_7\text{PS} + \text{H}$ ] $^+$ ; Anal Calcd for ( $\text{C}_{18}\text{H}_{23}\text{O}_7\text{PS} + 1.3\text{H}_2\text{O} + 0.1\text{EtOAc}$ ): C, 49.48; H, 5.96. Found: C, 49.18; H, 5.67.

### Example 54:

**Compound 54:** [3,5-Dimethyl-4-(4'-hydroxy-3'-*iso*-propylphenoxy)benzenesulfonyl]methylphosphonic acid



Step a:

[0919] To a stirring solution of (2,6-dimethyl-4-methylsulfonylphenoxy)triisopropylsilane (2.18 g, 6.72 mmol) in  $\text{CCl}_4$  (25 mL) at room temperature was added *N*-chlorosuccinimide (0.99 g, 7.39 mmol). The

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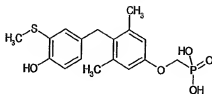
reaction mixture was stirred at room temperature for 16 hrs and filtered through a Celite plug. The solvent was removed under reduced pressure to afford crude (4-chloromethylsulfanyl-2,6-dimethylphenoxy)triisopropylsilane as an oil (2.4 g, 100%). This crude oil was dissolved into phosphorous acid triethyl ester (1.5 mL). It was heated at 180 °C for 30 min by microwave. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:1) to afford diethyl (3,5-dimethyl-4-triisopropylsilyloxy-phenylsulfanyl)methylphosphonate as a yellow oil (1.6 g, 52%); <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 7.09 (s, 2 H), 4.98 (m, 4 H), 3.31 (d, *J* = 13.8 Hz, 2 H), 2.17 (s, 6 H), 1.25 (m, 9 H), 1.09 (d, *J* = 7.0 Hz, 18 H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate/Hexanes (2:3); R<sub>f</sub> = 0.45.

## Step b:

[0920] The title compound was prepared according to the procedure described for the synthesis of example 53, steps e, f and g: <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.91 (s, 1 H), 7.16 (s, 2 H), 6.64 (m, 2 H), 6.21 (dd, *J* = 3.3, 8.7 Hz, 1 H), 4.13 (m, 3 H), 2.02 (s, 6 H), 1.11 (d, *J* = 6.9 Hz, 6 H); LC-MS *m/z* = 383 [C<sub>18</sub>H<sub>23</sub>O<sub>5</sub>PS + H]<sup>+</sup>; Anal Calcd for (C<sub>18</sub>H<sub>23</sub>O<sub>5</sub>PS + 0.15TFA + 0.2Et<sub>2</sub>O): C, 55.00; H, 5.98. Found: C, 54.88; H, 5.76.

## Example 55

**Compound 55:** [3,5-Dimethyl-4-(4'-hydroxy-3'-methylsulfanyl-benzyl)-phenoxy]methylphosphonic acid



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Step a:

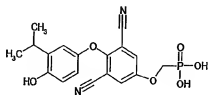
- [0921] To a stirring solution of diethyl [3,5-dimethyl-4-(3'-amino-4'-methoxymethoxybenzyl)phenoxy]methylphosphonate (Example 51, step a; 0.29g, 0.66 mmol) at 80 °C in dimethyldisulfide (3 mL) was added isoamyl nitrite (0.4 mL, 2.64 mmol). The reaction mixture was stirred at 80 °C for 1 h. The solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:1) to afford diethyl [3,5-dimethyl-4-(3'-methylsulfanyl-4'-methoxymethoxybenzyl)phenoxy]methylphosphonate as a red oil (0.12 g, 39%): <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 6.91 (d, *J* = 8.4 Hz, 1 H), 6.86 (d, *J* = 2.1 Hz, 1 H), 6.75 (s, 2 H), 6.58 (dd, *J* = 2.2, 8.4 Hz, 1 H), 5.16 (s, 2 H), 4.36 (d, *J* = 10.0 Hz, 2 H), 4.11 (m, 4 H), 3.89 (s, 2 H), 3.37 (s, 3 H), 2.30 (s, 3 H), 2.17 (s, 6 H), 1.25 (t, *J* = 7.0 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = 50% ethyl acetate in hexanes; *R*<sub>f</sub> = 0.61.

Step b:

- [0922] The title compound was prepared according to the procedure described for the synthesis of example 8, step f as a yellow foam (40 mg, 42%). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.58 (s, 1 H), 6.80 (d, *J* = 2.1 Hz, 1 H), 6.72 (s, 2 H), 6.66 (d, *J* = 8.4 Hz, 1 H), 6.50 (dd, *J* = 2.1, 8.4 Hz, 1 H), 4.06 (d, *J* = 10.2 Hz, 2 H), 3.84 (s, 2 H), 2.28 (s, 3 H), 2.18 (s, 6 H); LC-MS *m/z* = 369 [C<sub>17</sub>H<sub>21</sub>O<sub>5</sub>PS + H]<sup>+</sup>; Anal Calcd for (C<sub>17</sub>H<sub>21</sub>O<sub>5</sub>PS + 0.1EtOAc + 0.1TFA): C, 54.40; H, 5.68. Found: C, 54.65; H, 5.33.

## Example 56:

**Compound 56:** 3,5-Dicyano-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenoxy]methylphosphonate



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## Step a:

[0923] To a solution of 4-benzoyloxyphenol (0.2 g, 0.93 mmol) in dichloromethane (9.3 mL) at 0 °C was added bis(pyridine)iodonium tetrafluoroborate (0.76 g, 2.06 mmol). The reaction mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:9) to afford 4-benzoyloxy-3,5-diiodophenol as an off-white solid (0.22 g, 50%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.60 (s, 1 H), 8.06 (m, 2 H), 7.72 (s, 2 H), 7.59 (m, 3 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-acetone (4:1); R<sub>f</sub> = 0.45.

## Step b:

[0924] To a mixture of bis(4-methoxy-3-*iso*-propylphenyl)iodonium tetrafluoroborate (0.77 g, 1.51 mmol) and copper powder (0.13 g, 2.01 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4.4 mL) at 0 °C was added a solution of TEA (0.15 mL, 1.10 mmol) and 4-benzoyloxy-3,5-diiodophenol (0.47 g, 1.00 mmol) in dichloromethane (4.0 mL). The reaction mixture was stirred at room temperature for 24 h and filtered through a Celite plug. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with acetone-hexanes (1:9) to afford 3,5-diiodo-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl benzoate as an off-white solid (0.61 g, 98%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.10 (m, 2 H), 7.96 (s, 2 H), 7.73 (m, 1 H), 7.60 (m, 2 H), 6.85 (d, *J* = 9.0 Hz, 1H), 6.73 (d, *J* = 3.0 Hz, 1H), 6.35 (m, 1 H), 3.74 (s, 3 H), 3.21 (m, 1 H), 1.13 (d, *J* = 6.0 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-acetone (1:9); R<sub>f</sub> = 0.42.

## Step c:

[0925] To a stirred solution of 3,5-diiodo-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl benzoate (0.4 g, 0.76 mmol) in DMF (5.0 mL) at rt was added CuCN (0.27 g, 3.0 mmol). The reaction mixture was heated at

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160 °C for 5 min under microwave irradiation, the reaction mixture was cool to room temperature and poured into 1N HCl (50 mL) and extracted with ethyl acetate (100 mLx2). The organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (3:7) to afford 3,5-dicyano-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenol as a viscous oil (105 mg, 35%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.35 (s, 2 H), 6.99 (d, *J* = 3.0 Hz, 1 H), 6.78 (d, *J* = 8.7 Hz, 1 H), 6.99 (dd, *J* = 3.0, 8.7 Hz, 1 H), 3.84 (s, 3 H), 3.38 - 3.30 (m, 1 H), 1.21 (d, *J* = 6.9 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (7:3); R<sub>f</sub> = 0.38.

Step d:

[0926] 3,5-dicyano-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenol was prepared according to the procedure described for the synthesis of compound 54, step d (132 mg, 32%): <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.38 (s, 2H), 6.81 (d, *J* = 3.0 Hz, 1H), 6.70 (d, *J* = 9.0 Hz, 1H), 6.52 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.26 (heptuplet, *J* = 7.0 Hz, 1H), 1.18 (d, *J* = 7.0 Hz, 6H); TLC conditions: Merck silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (1:1); R<sub>f</sub> = 0.35.

Step e:

[0927] Diethyl trifluoromethanesulfonyloxymethylphosphonate (148 mg, 0.5 mmol) was added to an heterogeneous mixture of 3,5-dicyano-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenol (132 mg, 0.45 mmol) and cesium carbonate (440 mg, 1.35 mmol) in DMF at rt. After stirring at rt for 1 week, the reaction mixture was diluted with ethyl acetate and the pH lowered to 1 with 1 N hydrochloric acid. The organics were washed with water then brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes/ethyl acetate 50/50 to 0/100) to give diethyl 3,5-dicyano-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenoxy]methylphosphonate (44 mg, 22%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.42 (s, 2H), 6.73 (d, *J* = 3.0 Hz, 1H), 6.68 (d, *J* = 9.0 Hz, 1H), 6.57 (dd, *J* = 9.0, 3.0 Hz, 1H), 4.35-4.20 (m, 6H), 3.23 (heptuplet, *J* = 7.0

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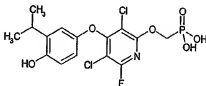
Hz, 1H), 1.38 (t,  $J = 7.0$  Hz, 6H), 1.18 (d,  $J = 7.0$  Hz, 6H); TLC conditions: Merck silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (1:1),  $R_f = 0.2$ .

Step f:

[0928] The title compound was prepared by the procedure described for the synthesis of compound 8, step f (18 mg, 47%):  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.74 (s, 2H), 6.85 (d,  $J = 3.0$  Hz, 1H), 6.72 (d,  $J = 9.0$  Hz, 1H), 6.56 (dd,  $J = 9.0, 3.0$  Hz, 1H), 4.35 (d,  $J = 6.8$  Hz 2H), 3.27 (heptuplet,  $J = 7.0$  Hz, 1H), 1.18 (d,  $J = 7.0$  Hz, 6H); Anal. Calcd for ( $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_6\text{P} + 1.4 \text{ H}_2\text{O}$ ): C, 52.28; H, 4.83; N, 6.77. Found: C, 52.55; H, 4.90; N, 6.12.

### Example 57

**Compound 57:** [4,6-dichloro-3-fluoro-5-(4'-hydroxy-3'-*iso*-propylphenoxy)-pyrid-2-yloxy]methyl phosphonic acid



Step a:

[0929] To a stirring solution of 3,5-dichloro-2,6-difluoro-4-(4'-methoxymethoxy-3'-*iso*-propyl-phenoxy)-pyridine (0.11 g, 0.29 mmol) and diethyl hydroxymethyl-phosphonate (0.045 mL, 0.31 mmol) in THF (3 mL) at  $0^\circ\text{C}$  was added NaH (13 mg, 0.31 mmol). The reaction mixture was stirred at room temperature for 16 hrs, diluted with EtOAc and washed with water (30 mLx2). The solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (2:1) to afford diethyl [4,6-dichloro-3-fluoro-5-(4'-hydroxy-3'-*iso*-propylphenoxy)-pyrid-2-yloxy]methyl phosphonate as a yellow oil (43 mg, 28%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.00 (d,  $J = 9.0$  Hz, 1 H), 6.96

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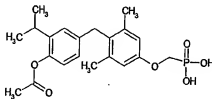
(d,  $J = 3.3$  Hz, 1 H), 6.67 (dd,  $J = 3.3, 9.0$  Hz, 1 H), 5.19 (s, 2 H), 4.77 (d,  $J = 8.1$  Hz, 2 H), 4.15 (m, 4 H), 3.40 (s, 3 H), 3.28 (m, 1 H), 1.27 (t,  $J = 7.2$  Hz, 6 H), 1.17 (d,  $J = 6.6$  Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = 66% ethyl acetate in hexanes;  $R_f = 0.31$ .

Step b:

[0930] The title compound was prepared according to the procedure described for the synthesis of example 8, step f as a white solid (30 mg, 71%): mp: 139-141 °C;  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  9.22 (s, 1 H), 6.84 (d,  $J = 2.8$  Hz, 1 H), 6.68 (d,  $J = 8.8$  Hz, 1 H), 6.47 (dd,  $J = 2.8, 8.8$  Hz, 1 H), 4.46 (d,  $J = 8.8$  Hz, 2 H), 3.17 (m, 1 H), 1.13 (d,  $J = 6.6$  Hz, 6 H); LC-MS  $m/z = 427$  [ $\text{C}_{15}\text{H}_{15}\text{C}_2\text{FNO}_6\text{P} + \text{H}^+$ ]; Anal Calcd for ( $\text{C}_{15}\text{H}_{15}\text{C}_2\text{FNO}_6\text{P} + 0.5\text{H}_2\text{O}$ ): C, 41.40; H, 3.71; N, 3.22. Found: C, 41.09; H, 3.87; N, 2.89.

### Example 58:

**Compound 58:** [4-(4'-Acetoxy-3'-*iso*-propylbenzyl)-3,5-dimethylphenoxy] methylphosphonic acid:



[0931] A mixture of [3,5-Dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)]phenoxy]methyl phosphonic acid (5.0 g, 13.7 mmol) and acetic anhydride (5.0 g, 48.9 mmol) in toluene (70 mL) was stirred at 20 °C for 3 hrs. Water (5 mL) was added and the mixture was stirred 1 hr. The solvent was removed under reduced pressure. Toluene (50 mL) was added to the residue then removed under reduced pressure. Toluene addition and evaporation was repeated twice more. The resulting solid was dried under vacuum at 45 °C to give the title compound (5.6 g, 100%). A purified sample (420 mg) was obtained by stirring the crude product in boiling isopropyl ether, cooling to 20 °C, collecting the solid by filtration, and drying under vacuum. mp: 169-172 °C;

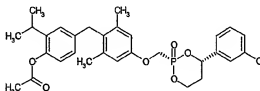


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<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.06 (d, *J* = 2.1 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.70 (s, 2H), 6.65 (dd, *J* = 9.0 and 2.4 Hz, 1H), 4.02 (d, *J* = 10.2 Hz, 2H), 3.90 (s, 2H), 2.94-2.84 (m, 1H), 2.25 (s, 3H), 2.15 (s, 6H), 1.07 (d, *J* = 6.9 Hz, 6H). Anal. Calcd for (C<sub>21</sub>H<sub>27</sub>O<sub>6</sub>P): C, 62.06; H, 6.70. Found: C, 62.22; H, 6.82.

### Example 59

*Cis* and *Trans* (S)-2-[[4-(4'-Acetoxy-3'-*iso*-propylbenzyl)-3,5-dimethylphenoxy]methyl]-4-(3-chlorophenyl)-2-oxo-2λ<sup>5</sup>-[1,3,2]-dioxaphosphonane:



[0932] A solution of oxalyl chloride (3.0 g, 23.6 mmol) in dichloromethane (14 mL) was added over 20 minutes to a stirring suspension of [4-(4'-acetoxy-3'-*iso*-propylbenzyl)-3,5-dimethylphenoxy]methylphosphonic acid (3.2 g, 7.88 mmol) in dichloromethane (50 mL). The resulting solution was stirred at 20 °C for 1hr. then the solvent was removed under reduced pressure. Dichloromethane (30 mL) was added to the residue then evaporated under reduced pressure. The resulting oil was dissolved in THF (32 mL) and the solution was added over 40 minutes to a stirring solution of (S)-1-(3-chlorophenyl)-1,3-propanediol (1.5 g, 7.88 mmol) and triethylamine (2.4 g, 23.6 mmol) in THF (32 mL) while keeping the temperature below -70 °C. The reaction mixture was stirred at -70 °C for 2 hrs. then warmed to 15 °C. To the reaction mixture was added 0.5 M aqueous HCl (32 mL) and ethyl acetate (32 mL). The phases were separated and the aqueous layer was extracted with ethyl acetate (32 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and filtered. The solvent was removed under reduced pressure. The crude product was purified by

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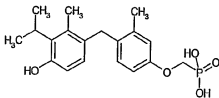
chromatography on silica gel, eluting with ethyl acetate-hexanes (50%-100%) to afford:

**Compound 59-trans:** (610 mg, 14%):  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  7.48-7.36 (m, 4H), 7.07 (d,  $J$  = 2.1 Hz, 1H), 6.85 (d,  $J$  = 8.4 Hz, 1H), 6.83 (s, 2H), 6.64 (dd,  $J$  = 9.0 and 2.0 Hz, 1H), 5.85-5.82, (m, 1H), 4.74-4.68 (m, 1H), 4.61 (d,  $J$  = 9.3 Hz, 2H), 4.52-4.42 (m, 1H), 3.92 (s, 2H), 2.94-2.85 (m, 1H), 2.25 (s, 3H), 2.24-2.20 (m, 2H), 2.17 (s, 6H), 1.07 (d,  $J$  = 6.9 Hz, 6H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = dichloromethane-acetone (9:1);  $R_f$  = 0.5.

**Compound 59-cis:** (2.5g, 57%):  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  7.47 (m, 1H), 7.38-7.26 (m, 3H), 7.06 (d,  $J$  = 2.1 Hz, 1H), 6.85 (d,  $J$  = 8.7 Hz, 1H), 6.76 (s, 2H), 6.67 (dd,  $J$  = 8.1 and 2.1 Hz, 1H), 5.76-5.72 (m, 1H), 4.61-4.36 (m, 4H), 3.92 (s, 2H), 2.94-2.85 (m, 1H), 2.25 (s, 3H), 2.20-2.19 (m, 2H), 2.16 (s, 6H), 1.07 (d,  $J$  = 6.9 Hz, 6H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = dichloromethane-acetone (9:1);  $R_f$  = 0.35; Anal Calcd for ( $\text{C}_{30}\text{H}_{34}\text{ClO}_6\text{P}$  + 0.13  $\text{H}_2\text{O}$ ): C, 64.42; H, 6.17. Found: C, 64.12; H, 6.07.

### Example 60

**Compound 60:** [4-(4'-Hydroxy-3'-*iso*-propyl-2'-methylbenzyl)-3-methylphenoxy]methylphosphonic acid



Step a:

[0933] To a stirring solution of 1-bromo-3-*iso*-propyl-4-methoxy-2-methylbenzene (compound 7-16, step c; 0.7 g, 2.88 mmol) in THF (20 mL) at  $-78^\circ\text{C}$  was added *n*-BuLi (1.6 mL, 2.5 M in hexanes). The mixture was stirred at  $-78^\circ\text{C}$  for 1 hr and 4-methoxy-2-methyl-benzaldehyde (0.37 mL, 2.74 mmol) was

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added. The reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 1 hr, allowed to warm to room temperature and stirred for 1 hr. The reaction mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  and diluted with diethyl ether. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to afford crude

(4'-methoxy-3'-*iso*-propyl-2'-methylphenyl)-(4-methoxy-2-methylphenyl)-methanol as a light yellow oil (1.0 g, 100%). This crude oil was dissolved into EtOAc (25 mL) and AcOH (5 mL) and Pd/C (0.1 g) was added. After stirring at rt for 6 hours, the reaction mixture was filtered through the Celite and concentrated under reduced pressure to afford crude 4-(4'-methoxy-2'-methyl-3'-*iso*-propylbenzyl)-3-methyl-anisole as a yellow oil (0.8 g, 93%);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  6.88–6.80 (m, 5 H), 3.77 (s, 2 H), 3.74 (s, 3 H), 3.71 (s, 3 H), 3.34 (m, 1 H), 2.22 (s, 3 H), 2.14 (s, 3 H), 1.28 (d,  $J = 6.9$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 8% ethyl acetate in hexanes;  $R_f = 0.56$ .

Step b:

[0934] To a stirring solution of 4-(4'-methoxy-2'-methyl-3'-*iso*-propylbenzyl)-3-methyl-anisole (0.8 g, 2.68 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at  $-20^{\circ}\text{C}$  was added  $\text{BBr}_3$  (10.7 mL, 1M in  $\text{CH}_2\text{Cl}_2$ ). The reaction mixture was stirred at room temperature for 16 hrs. Ice was add and the mixture was diluted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate/hexanes (1:1) to afford 4-(4'-hydroxy-2'-methyl-3'-*iso*-propylbenzyl)-3-methylphenol as a yellow solid (0.54 g, 75%);  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.03 (s, 1 H), 8.84 (s, 1 H), 6.41-6.60 (m, 5 H), 3.65 (s, 2 H), 3.33 (m, 1 H), 2.12 (s, 3 H), 2.08 (s, 3 H), 1.27 (d,  $J = 6.9$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 20% ethyl acetate in hexanes;  $R_f = 0.31$ .

Step c:

[0935] To a solution of 44-(4'-hydroxy-2'-methyl-3'-*iso*-propylbenzyl)-3-methylphenol (0.54 g, 2 mmol) in DMF (15 mL) at room temperature was

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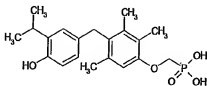
added  $\text{Cs}_2\text{CO}_3$  (2.6 g, 8 mmol) and diethyl trifluoromethanesulfonyloxymethylphosphonate (0.66 g, 2.2 mmol). The reaction mixture was stirred at room temperature for 1 hr. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and saturated  $\text{NaHCO}_3$ . The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (4:1) to afford diethyl [4-(4'-hydroxy-3'-*iso*-propyl-2'-methylbenzyl)-3-methylphenoxy]methylphosphonate as a colorless oil (0.14 g, 17%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.89 (s, 1 H), 6.86 (d,  $J = 2.7$  Hz, 1 H), 6.76 (dd,  $J = 2.7, 9.0$  Hz, 1 H), 6.67 (d,  $J = 9.0$  Hz, 1 H), 6.51 (m, 2 H), 4.36 (d,  $J = 9.6$  Hz, 2 H), 4.11 (m, 4 H), 3.73 (s, 2 H), 3.34 (m, 1 H), 2.22 (s, 3 H), 2.09 (s, 3 H), 1.27 (m, 12 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 66% ethyl acetate in hexanes;  $R_f = 0.45$ .

Step d:

[0936] The title compound was prepared according to the procedure described for the synthesis of example 8, step f as a white solid (80 mg, 67%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ): 8.88 (s, 1 H), 6.85 (d,  $J = 2.1$  Hz, 1 H), 6.73 (dd,  $J = 2.1, 8.7$  Hz, 1 H), 6.66 (d,  $J = 8.7$  Hz, 1 H), 6.51 (m, 2 H), 4.02 (d,  $J = 10.2$  Hz, 2 H), 3.73 (s, 2 H), 3.34 (m, 1 H), 2.22 (s, 3 H), 2.10 (s, 3 H), 1.30 (d,  $J = 6.9$  Hz, 6 H); mp: 166 – 168 °C; LC-MS  $m/z = 363$  [ $\text{C}_{19}\text{H}_{25}\text{O}_5\text{P} - \text{H}$ ]; Anal Calcd for ( $\text{C}_{19}\text{H}_{25}\text{O}_5\text{P} + 0.13\text{HBr}$ ): C, 60.87; H, 6.76; Br, 2.77. Found: C, 61.19; H, 6.84; Br, 3.10.

### Example 61:

**Compound 61-1:** [4-(4'-hydroxy-3'-*iso*-propylbenzyl)-2,3,5-trimethylphenoxy]methylphosphonic Acid



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## Step a:

[0937] A mixture of 3,5-dimethyl-2-iodo-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenol (compound 47, step a; 1.0 g, 2.27 mmol) and  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.10 g, 0.14 mmol) in TEA (1.6 mL) and methanol (8.0 mL) was heated under a CO atmosphere (60 psi) at 80 °C for 72 h. The reaction mixture was cooled to room temperature and filtered through a Celite plug. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel, eluting with 10% ethyl acetate in hexanes to afford methyl 2,4-dimethyl-6-hydroxy-3-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)benzoate (0.32 g, 38 %):  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  6.93 (m, 2 H), 6.67 (s, 2 H), 5.18 (s, 1 H), 3.98 (s, 2 H), 3.92 (s, 3 H), 3.48 (s, 3 H), 3.30 (m, 1 H), 2.22 (m, 6 H), 1.18 (d,  $J = 6.9$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:5);  $R_f = 0.60$ .

## Step b:

[0938] To a solution of methyl 2,4-dimethyl-6-hydroxy-3-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)benzoate in ethanol-water (3.0 mL, 95:5) at room temperature was added  $\text{NaBH}_4$ . The reaction mixture was heated at 80 °C for 4 h and cooled to room temperature. The reaction mixture was quenched with aqueous  $\text{NH}_4\text{Cl}$  and extracted with ether. The organic layer was dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with 30% acetone in hexanes to afford 2,4-dimethyl-6-hydroxy-3-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)benzyl alcohol:  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  6.97 (d,  $J = 2.4$  Hz, 1 H), 6.92 (d,  $J = 13.2$  Hz, 1 H), 6.68 (dd,  $J = 13.2, 2.4$  Hz, 1 H), 6.59 (s, 1 H), 5.17 (s, 2 H), 4.78 (s, 2 H), 3.96 (s, 2 H), 3.47 (s, 3 H), 3.30 (m, 1 H), 2.24 (s, 3 H), 2.19 (s, 3 H), 1.18 (d,  $J = 10.8$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = acetone-hexanes (3:7);  $R_f = 0.40$ .

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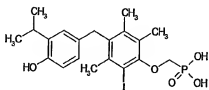
Step c:

[0939] A mixture of 2,4-dimethyl-6-hydroxy-3-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)benzyl alcohol ((0.20 g, 0.58 mmol) and Pd-C (0.08 g, 10%) in ethyl acetate-acetic acid (3.5 mL, 95:5) was stirred at room temperature under a H<sub>2</sub> atmosphere for 6 h. The reaction mixture was filtered through a Celite plug and the solvent was removed under reduced pressure to afford 4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)-2,3,5-trimethylphenol (0.19 g, 100%) as colorless oil: <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 6.94 (m, 1 H), 6.91 (d, *J* = 13.2 Hz, 1 H), 6.68 (dd, *J* = 13.2, 2.4 Hz, 1 H), 6.55 (s, 1 H), 5.17 (s, 2 H), 3.95 (s, 2 H), 3.47 (s, 3 H), 3.30 (m, 1 H), 2.19 (s, 3 H), 2.16 (s, 3 H), 2.11 (s, 3 H), 1.17 (d, *J* = 10.8 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = acetone-hexanes (3:7); R<sub>f</sub> = 0.60.

[0940] The title compound was prepared according to the procedure described for the synthesis of compound 7: mp: 56.0-58.0 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 6.85 (d, *J* = 2.4 Hz, 1 H), 6.76 (s, 1 H), 6.60 (d, *J* = 12.0 Hz, 1 H), 6.52 (dd, *J* = 12.6, 2.4 Hz, 1 H), 4.22 (d, *J* = 10.2 Hz, 2 H), 3.94 (s, 2 H), 3.23 (m, 1 H), 2.25 (s, 3 H), 2.24 (s, 3 H), 2.15 (s, 3 H), 1.17 (d, *J* = 10.8 Hz, 6 H); LC-MS *m/z* = 379 [C<sub>20</sub>H<sub>27</sub>O<sub>5</sub>P + H]<sup>+</sup>; Anal Calcd for [C<sub>20</sub>H<sub>27</sub>O<sub>5</sub>P + 1.1 H<sub>2</sub>O]: C, 60.32; H, 7.39. Found: C, 60.05; H, 7.14.

### Example 62

**Compound 62:** [6-iodo-4-(4'-hydroxy-3'-*iso*-propylbenzyl)-2,3,5-trimethylphenoxy]methylphosphonic Acid



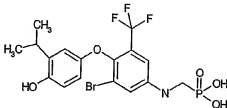
[0941] [6-Iodo-4-(4'-hydroxy-3'-*iso*-propylbenzyl)-2,3,5-trimethylphenoxy]methylphosphonic acid was prepared from 4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)-2,3,5-trimethylphenol (compound 61-1, step c) was prepared according to the procedure described for the synthesis of compound

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45, step a and transformed into the title compound according to the procedure described for the synthesis of compound 7-1: mp: 185-187 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  6.88 (d,  $J = 2.4$  Hz, 1 H), 6.61 (d,  $J = 12.3$  Hz, 1 H), 6.50 (d,  $J = 2.4$  Hz, 1 H), 4.14 (d,  $J = 10.5$  Hz, 1 H), 4.09 (s, 2 H), 3.24 (m, 1 H), 2.46 (s, 3 H), 2.39 (s, 3 H), 2.19 (s, 3 H), 1.18 (d,  $J = 6.9$  Hz, 6 H); LC-MS  $m/z = 504$  [ $\text{C}_{20}\text{H}_{27}\text{O}_5\text{P}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{20}\text{H}_{26}\text{IO}_5\text{P} + 0.8 \text{ H}_2\text{O}$ ): C, 46.26; H, 5.41. Found: C, 46.48; H, 5.78.

### Example 63

**Compound 63:** [3-Bromo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)-5-trifluoromethyl-phenylamino]methylphosphonic acid



Step a:

[0942] Intermediate 1,5-dibromo-2-(3'-*iso*-propyl-4'-methoxy-phenoxy)-3-trifluoromethyl-benzene was prepared from 2,4-dibromo-6-trifluoromethyl-phenol (*J. Amer. Chem. Soc.*, **1947**, 2346) according to the procedure described for the synthesis of compound 4, step a:  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.39 (m, 1 H), 8.07 (m, 1 H), 6.85 (m, 2 H), 6.45 (m, 1 H), 3.73 (s, 3 H), 3.15 (m, 1 H), 1.08 (d,  $J = 10.5$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes;  $R_f = 0.54$ .

Step b:

[0943] To a mixture of  $\text{Pd}(\text{OAc})_2$  (0.031 g, 0.14 mmol) in toluene (40 mL) at rt was added (+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.13 mL, 0.21 mmol). The reaction mixture was stirred at rt for several minutes and  $\text{Cs}_2\text{CO}_3$  (3.62 g, 11.10 mmol), 1,5-dibromo-2-(3'-*iso*-propyl-4'-methoxyphenoxy)-3-trifluoromethyl-benzene (1.30 g, 2.77 mmol, dissolved in 10 mL toluene), and

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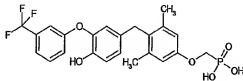
diethyl aminomethylphosphonate oxalate (0.76 g, 2.97 mmol) were added. The reaction mixture was stirred at 100 °C for 16 h. The solution was cooled to rt, diluted with diethyl ether (25 mL), filtered and concentrated. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:1) to afford diethyl [3-bromo-4-(4'-methoxy-3'-isopropyl-phenoxy)-5-trifluoromethylphenylamino]methylphosphonate as an oil (0.28 g, 18%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.33 (m, 1 H), 7.16 (m, 1 H), 6.85 (m, 1 H), 6.65 (m, 1 H), 6.55 (m, 1 H), 6.39 (m, 1 H), 4.08 (m, 4 H), 3.74 (s, 3 H), 3.68 (m, 2 H), 3.21 (m, 1 H), 1.19 (m, 6 H), 1.11 (d, J = 6.0 Hz, 6 H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (4:1); R<sub>f</sub> = 0.25.

Step c:

[0944] The title compound was prepared according to the procedure described for the synthesis of Example 19, step e: mp: 98-102 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.11 (m, 1 H), 6.95 (m, 2 H), 6.48 (m, 1 H), 6.45 (m, 1 H), 6.20 (m, 1 H), 3.41 (d, *J* = 12.0 Hz, 2 H), 3.12 (m, 1 H), 1.17 (m, 18 H), 1.04 (d, *J* = 6.0 Hz, 6 H); LC-MS *m/z* = 484 [C<sub>17</sub>H<sub>18</sub>BrF<sub>3</sub>NO<sub>3</sub>P - H]<sup>+</sup>; HPLC conditions: Column = Shimadzu LC-A8, SPD-10A; YMC Pack RP-18 filter, 150×4.6; Mobile phase = Solvent A Acetonitrile/0.05% TFA; Solvent B = H<sub>2</sub>O/0.05% TFA. Gradient: 0min: 20% B; 13 min: 70% B; 16min: 100% B; 18min: 20% B. Flow rate = 2.0 mL/min; UV@ 254 nm. rt = 9.16min.

### Example 64

**Compound 64:** [3,5-Dimethyl-4-[4'-hydroxy-3'-(3-trifluoromethylphenoxy)benzyl]phenoxy]methylphosphonic acid





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Step a:

[0945] To 5-(2,6-dimethyl-4-triisopropylsilyloxybenzyl)-2-methoxy methoxy-benzaldehyde (compound 15, step c; 0.460 g, 1.01mmol) in dichloromethane 30 mL was add mCPBA (0.870 g, 2.52 mmol) and saturated sodium bicarbonate solution (2 mL). After stirring at rt overnight, the reaction mixture was poured into dichloromethane 50 mL and washed 3 x with 10 mL of saturated aqueous sodium bicarbonate. The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was combined with methanol (10 mL) and 2 mL of 1 N NaOH and stirred for 1.5 hours at room temperature. The reaction was acidified with 12 N HCl (pH<3) and poured into 50 mL ethyl acetate. The layers were separated and the organics were dried over sodium sulfate, filtered and concentrated. Flash column chromatography using silica and a step gradient of hexane/ethyl acetate [20:1], hexane/ethyl acetate [9:1] provided 5-(2,6-dimethyl-4-triisopropylsilyloxybenzyl)-2-methoxymethoxy-phenol (0.189 g, 42%):  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  8.95(s, 1H), 6.86(d, 1H,  $J$  = 8.1 Hz), 6.56(s, 2H), 6.41(d, 1H,  $J$  = 2.1 Hz), 6.34(dd, 1H,  $J$  = 2.1 Hz and  $J$  = 8.7 Hz), 5.05(s, 2H), 3.78(s, 2H), 3.38(s, 3H), 2.13(s, 6H), 1.11(m, 3H), 1.00(m, 18H); Uniplat silica gel, 250 microns; Mobile phase = 10% ethyl acetate in hexane: Rf = 0.15

Step b:

[0946] (2,6-Dimethyl-4-triisopropylsilyloxybenzyl)-4-methoxymethoxy-3-(3-trifluoromethylphenoxy)benzene was prepared from 5-(2,6-dimethyl-4-triisopropylsilyloxybenzyl)-2-methoxymethoxy-phenol according to the procedure described in Dominic M. T. Chan *et al. Tetrahedron Lett.* 1998, 39, 2933-2936, (0.070 g, 37%)  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  7.53(t, 1H,  $J$  = 7.8 Hz), 7.35(d, 1H,  $J$  = 7.8 Hz), 7.21-7.10(m, 2H), 6.98(s, 1H), 6.89(m, 1H), 6.59(m, 1H), 6.64(s, 2H), 5.09(s, 2H), 3.89(s, 2H), 3.18(s, 3H), 2.11(s, 6H), 1.16(m, 3H), 1.01(m, 18H); Uniplat silica gel, 250 microns; Mobile phase = 10% ethyl acetate in hexane: Rf = 0.47

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Step c:

- [0947] 3,5-Dimethyl-4-[4'-methoxymethoxy-3'-(3-trifluoromethylphenoxy)benzyl]phenol was synthesized according to the procedure described for the synthesis of compound 35, step e, (0.059 g, 100%); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.02(s, 1H), 7.55(t, 1H, *J* = 7.8 Hz), 7.38(1H, d, *J* = 8.4 Hz), 7.14(m, 2H), 7.02(s, 1H), 6.88(dd, 1H, *J* = 1.5 Hz and *J* = 6.6 Hz), 6.72(d, 1H, 2.1 Hz), 6.44(s, 2H), 5.08(s, 2H), 3.85(s, 2H), 3.18(s, 3H), 2.08(s, 6H); (Uniplat silica gel, 250 microns; Mobile phase = 25% ethyl acetate in hexane: R<sub>f</sub> = 0.28

Step d:

- [0948] Diethyl[3,5-dimethyl-4-[4'-methoxymethoxy-3'-(3-trifluoromethylphenoxy)benzyl]phenoxy]methylphosphonate was prepared according to the procedure described for the synthesis of compound 8, steps e (0.015 g, 15%); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.55(t, 1H, *J* = 8.4 Hz), 7.37(d, 1H, *J* = 7.5 Hz), 7.14(m, 2H), 7.02(s, 1H), 6.86(dd, 1H, *J* = 1.7 Hz and *J* = 7 Hz), 6.73(s, 2H), 5.08(s, 2H), 4.34(d, 2H, *J* = 9.9 Hz), 4.09(m, 4H), 3.91(s, 2H), 3.18(s, 3H), 2.18(s, 6H), 1.24(t, 6H, *J* = 7 Hz); Uniplat silica gel, 250 microns; Mobile phase = 25% hexane in ethyl acetate: R<sub>f</sub> = 0.2

Step e:

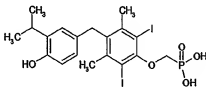
- [0949] The title compound was prepared according to the procedure described for the synthesis of compound 8, steps f, (0.022g, 90%); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.48(s, 1H), 7.53(t, 1H, *J* = 7.8 Hz), 7.34(d, 1H, *J* = 7.2 Hz), 7.07(d, 1H, *J* = 9 Hz), 7.01(s, 1H), 6.90(d, 1H, *J* = 8.4 Hz), 6.71(m, 4H), 4.00(d, 2H, *J* = 10.2 Hz), 3.84(s, 2H), 2.15(s, 6H); LC-MS *m/z* = 481 [C<sub>22</sub>H<sub>22</sub>F<sub>3</sub>O<sub>6</sub>P - H]<sup>+</sup>; Uniplat silica gel, 250 microns; Mobile phase = isopropyl alcohol /water/ ammonium hydroxide [7:2:1]: R<sub>f</sub> = 0.47; HPLC, zorbax, XDB-C8, 150mm x 4.6 mm, 5μm, flow 1 mL/min, solvent A: 0.05 M KH<sub>2</sub>PO<sub>4</sub> aqueous pH 6.2, Solvent B: acetonitrile, Gradient 40% B to 60%B over 11min then 60%B. total run time 12 min. RT 1.87 min; Anal Calcd for

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(C<sub>23</sub>H<sub>22</sub>F<sub>3</sub>O<sub>6</sub>P + 0.3 M H<sub>2</sub>O + 0.1 M EtOAc) C, 56.60; H, 4.70. Found: C, 56.68; H, 3.97.

### Example 65

**Compound 65-1:** 2,6-diiodo-3,5-dimethyl-4-[4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methyl phosphonic acid



#### Step a:

[0950] To a stirred solution of 3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenol (0.22 g, 0.70 mmol), (Chiellini *et al.*, *Bioorg. Med. Chem. Lett.* 10:2607 (2000)) in EtOH (6.2 mL) and CH<sub>3</sub>NH<sub>2</sub> 40% in water (2.5 mL) was added iodine (0.39 g, 1.54 mmol) and KI (0.25 g 1.54 mmol) in H<sub>2</sub>O (3 mL) at 0° C. The reaction mixture was stirred at room temperature for 16 h, quenched with brine (50 mL) and extracted with ethyl acetate (50 mLx2). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:4) to afford 2,6-diiodo-3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenol as a colorless oil (198 mg, 50%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 6.97 (d, *J* = 2.1 Hz, 1 H), 6.92 (d, *J* = 5.6 Hz, 1 H), 6.59 (dd, *J* = 2.4, 8.4 Hz, 1 H), 6.0 (s, 1 H), 5.19 (s, 2 H), 4.16 (s, 2 H), 3.50 (s, 3 H), 3.35 - 3.30 (m, 1 H), 2.48 (s, 6 H), 1.21 (d, *J* = 6.9 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (4:1); R<sub>f</sub> = 0.62.

#### Step b:

[0951] To a stirred solution of 2,6-diiodo-3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)phenol (0.2 g, 0.35 mmol) in DMF (3.0 mL) at 0 °C

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was added  $\text{Cs}_2\text{CO}_3$  (0.34 g, 1.05 mmol). After 10-min, diethyl trifluoromethanesulfonyloxymethyl phosphonate (0.1 g, 0.35 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h, allowed to warm to room temperature and stirred for 16 h. The reaction mixture was quenched with 1 N HCl, diluted with ethyl acetate, and washed with water (10 mLx4) and brine. The organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (2:3) as mobile phase to afford diethyl [2,6-diiodo-3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)phenoxy]methylphosphonate as an oil (0.21 g, 85%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.96 (d,  $J = 2.4$  Hz, 1 H), 6.92 (d,  $J = 8.4$  Hz, 1 H), 6.56 (dd,  $J = 2.1, 8.4$  Hz, 1 H), 5.18 (s, 2 H), 4.45 - 4.35 (m, 6 H), 4.18 (s, 2H), 3.50 (s, 3H), 3.39 - 3.25 (m, 1 H), 2.49 (s, 6 H), 1.47 (t,  $J = 6.9$  Hz, 6 H), 1.20 (d,  $J = 6.9$  Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (1:1);  $R_f = 0.35$ .

#### Step c:

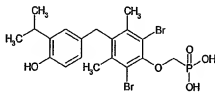
[0952] To a solution of diethyl [2,6-diiodo-3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)phenoxy]methylphosphonate (0.14 g, 0.19 mmol) in  $\text{CH}_2\text{Cl}_2$  (4.0 mL) at 0 °C was added bromotrimethylsilane (0.31 mL, 1.9 mmol). The reaction mixture was stirred at room temperature for 16 h and the solvent was removed under reduced pressure. The residue was treated with methanol and water (4:1, 5.0 mL) and the solvents were removed under reduced pressure. The residue was treated with acetonitrile and filtered to afford 2,6-diiodo-3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methyl phosphonic acid as white solid (97 mg, 80%): mp 236 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  6.87 (s, 1 H), 6.62 (d,  $J = 7.8$  Hz, 1 H), 6.46 (d,  $J = 8.7$  Hz, 1 H), 4.31 (d,  $J = 10.8$  Hz, 2 H), 4.19 (s, 2 H), 3.35 - 3.18 (m, 1 H), 2.50 (s, 6 H), 1.17 (d,  $J = 6.9$  Hz, 6 H); LC-MS  $m/z = 616$  [ $\text{C}_{19}\text{H}_{23}\text{I}_2\text{O}_5\text{P}$ ] $^+$ ; HPLC conditions: ODSAQ AQ-303-5 column; mobile phase =  $\text{CH}_3\text{OH}$ :0.05%TFA(7:3) flow rate = 1.0 mL/min; detection = UV @ 280 nm

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retention time in min: 13.82; Anal Calcd for (C<sub>20</sub>H<sub>25</sub>O<sub>6</sub>P + 0.9 H<sub>2</sub>O): C, 36.09; H, 3.95. Found: C, 35.80; H, 4.22.

[0953] Using the appropriate starting material, compounds 65-2 was prepared in an analogous manner to that described for the synthesis of compound 65-1.

**Compound 65-2:** 2,6-dibromo-3,5-dimethyl-[4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methyl phosphonic acid



Step a

[0954] To a stirred solution of 3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenol (0.2 g, 0.63 mmol), (Chiellini *et al.*, *Bioorg. Med. Chem. Lett.* 10:2607 (2000)) in EtOH (6.0 mL) and CH<sub>3</sub>NH<sub>2</sub> 40% in water (2.5 mL) was added bromine (0.25 g, 1.59 mmol) and KBr (0.11 g 1.59 mmol) in H<sub>2</sub>O (2 mL) at 0° C. The reaction mixture was stirred at room temperature for 16 h, quenched with water (50 mL) and extracted with ethyl acetate (50 mLx2). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:9) to afford 2,6-dibromo-3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenol as a white solid (0.18 g, 60%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 6.97 (d, *J* = 2.1 Hz, 1 H), 6.92 (d, *J* = 8.4 Hz, 1 H), 6.60 (dd, *J* = 2.4, 8.7 Hz, 1 H), 6.0 (s, 1 H), 5.19 (s, 2 H), 4.08 (s, 2 H), 3.50 (s, 3 H), 3.35 - 3.30 (m, 1 H), 2.38 (s, 6 H), 1.21 (d, *J* = 6.0 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (4:1); R<sub>f</sub> = 0.62.

Step b:

[0955] The title compound was prepared according to the procedure described for the synthesis of example 45, step b and c: as a white solid (0.15 g, 80%)

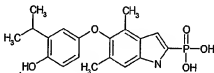
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mp 190 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  6.88 (d,  $J = 2.1$  Hz, 1 H), 6.62 (d,  $J = 8.4$  Hz, 1 H), 6.46 (dd,  $J = 2.4, 8.7$  Hz, 1 H), 4.27 (d,  $J = 10.5$  Hz, 2 H), 4.12 (s, 2 H), 3.35 - 3.18 (m, 1 H), 2.40 (s, 6 H), 1.17 (d,  $J = 6.9$  Hz, 6 H); LC-MS  $m/z = 523$  [ $\text{C}_{19}\text{H}_{23}\text{I}_2\text{O}_5\text{P} + \text{H}$ ] $^+$ ; HPLC conditions: ODSAQ AQ-12S05146W column; mobile phase = 0.05%TFA/ $\text{CH}_3\text{CN}$ :0.05%TFA/ $\text{H}_2\text{O}$

[0956] (1:1) flow rate = 1.0 mL/min; detection = UV @ 254 nm retention time in min: 10.45; Anal Calcd for ( $\text{C}_{20}\text{H}_{23}\text{Br}_2\text{O}_5\text{P}$ ): C, 43.70; H, 4.44. Found: C, 43.78; H, 4.46.

### Example 66

**Compound 66:** 4,6-Dimethyl-4-(4'-hydroxy-3'-*iso*-propylphenoxy) indolephosphonic acid



Step a:

[0957] A solution of sodium nitrite (155 mg, 2.24 mmol) in water (1 mL) was added to a suspension of 3,5-dimethyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)-aniline (*J. Med. Chem.* 38:695 (1995), 640 mg, 2.24 mmol) in ethanol (3mL) and concentrated hydrochloric acid (12 M, 1.12 mL, 13.44 mmol) at 0 °C. The yellow heterogeneous solution slowly turns to an orange clear solution. After stirring at 0 °C for 30 minutes, a solution of tin dichloride (1.53 g, 8.06 mmol) in hydrochloric acid (12 M, 1.3 mL, 15.68 mmol) was added. The orange solution turned green and a white precipitate formed. Ethanol (3 mL) was added to dissolve most of the precipitate and the heterogeneous reaction mixture was stirred at 0 °C. After 2 hours, water was added and the precipitate collected by filtration. The sticky solid was dissolved in ethyl acetate and washed with water, 1 N sodium hydroxide then brine. The organics were dried over sodium sulfate, concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, dichloromethane/methanol

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95/5 to 90/10) to give 3,5-dimethyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)-phenyl hydrazine (305 mg, 45%);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.77 (d,  $J$  = 3.0 Hz, 1H), 6.67 (d,  $J$  = 9.0 Hz, 1H) 6.58 (s, 2H), 6.37 (dd,  $J$  = 9.0, 3.0 Hz, 1H), 3.77 (s, 3H), 3.27 (heptuplet,  $J$  = 6.9 Hz, 1H), 2.09 (s, 3H), 1.18 (d,  $J$  = 6.9 Hz, 6H); TLC conditions: Merck silica gel, 250 microns; Mobile phase = dichloromethane-methanol (9:1);  $R_f$  = 0.6.

Step b:

[0958] Diethyl acetylphosphonate (183 mg, 1.02 mmol) was added to a yellow solution of hydrazine in toluene at rt. After stirring 10 minutes at rt, polyphosphoric acid (PPA, 0.4 g) was added and the turbid reaction mixture was placed in an oil bath at 115 °C. After refluxing for 5 minutes, the cooled brown biphasic solution was partitioned between ethyl acetate and water and the organic layer was washed with water then brine, dried over sodium sulfate, concentrated under reduced pressure and the residue purified by column chromatography (silica gel, hexanes/ethyl acetate 70/30 to 20/80) to give diethyl 5,6-dimethyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)indolephosphonate (276 mg, 61%);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (s, 1H, exchangeable with  $\text{D}_2\text{O}$ ), 7.17 (s, 1H), 7.07 (m, 1H), 6.83 (d,  $J$  = 3.0 Hz, 1H), 6.65 (d,  $J$  = 9.0 Hz, 1H), 6.34 (dd,  $J$  = 9.0, 3.0 Hz, 1H), 4.30-4.08 (m, 4H), 3.77 (s, 3H), 3.28 (heptuplet,  $J$  = 6.9 Hz, 1H), 2.35 (s, 3H), 2.24 (s, 3H), 1.37 (t,  $J$  = 7.1 Hz, 6H), 1.18 (d,  $J$  = 6.9 Hz, 6H); TLC conditions: Merck silica gel, 250 microns; Mobile phase = dichloromethane-methanol (9:1);  $R_f$  = 0.55.

Step c:

[0959] 5,6-Dimethyl-4-(4'-hydroxy-3'-*iso*-propylphenoxy)indolephosphonic acid was prepared according to the procedure described for the synthesis of example 8, step f (100 mg, 51%);  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.14 (s, 1H), 6.97 (s, 1H), 6.75 (d,  $J$  = 9.0 Hz, 1H), 6.68 (d,  $J$  = 3.0 Hz, 1H), 6.35 (dd,  $J$  = 9.0, 3.0 Hz, 1H), 3.75 (s, 3H), 3.25 (heptuplet,  $J$  = 6.9 Hz, 1H), 2.27 (s, 3H), 2.16 (s, 3H), 1.11 (d,  $J$  = 6.9 Hz, 6H); LC-MS  $m/z$  = 390.4 [ $\text{C}_{20}\text{H}_{24}\text{NO}_3\text{P} + \text{H}$ ] $^+$ .

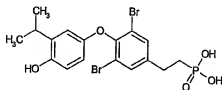
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Step d:

[0960] A solution of boron tribromide (1 M in dichloromethane, 1.3 mL, 1.3 mmol) was added to a solution of 5,6-dimethyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)indolephosphonic acid (100 mg, 0.26 mmol) in dichloromethane (10 mL) at -78 °C. The ice bath was removed and the reaction mixture was warmed to rt. After stirring at rt overnight, the reaction mixture was quenched with ice, diluted with ethyl acetate and washed with water then brine, dried over sodium sulfate and concentrated under reduced pressure to give the title compound (86.3 mg, 80%): <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.18 (s, 1H), 6.97 (d, *J* = 3.0 Hz, 1H), 6.60 (s, 1H), 6.57 (d, *J* = 9.0 Hz, 1H), 6.26 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.22 (heptuplet, *J* = 6.9 Hz, 1H), 2.28 (s, 3H), 2.18 (s, 3H), 1.12 (d, *J* = 6.9 Hz, 6H); Anal. Calcd for (C<sub>19</sub>H<sub>22</sub>NO<sub>5</sub>P + 1.5 H<sub>2</sub>O + 0.1 C<sub>3</sub>H<sub>8</sub>O): C, 56.79; H, 6.32; N, 3.43. Found: C, 56.61; H, 5.92; N, 3.22.

## Example 67

**Compound 67:** 2-[3,5-dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)phenyl]ethylphosphonic Acid



Step a:

[0961] To a solution of dimethyl methylphosphonate (0.06 g, 0.48 mmol) in THF (3.0 mL) at -78 °C was slowly added LDA (0.25 mL, 2 M in THF). After 30 min, a solution of 3,5-dibromo-4-(3'-isopropyl-4'-methoxyphenoxy)benzyl bromide (0.20 g, 0.40 mmol, intermediate for the synthesis of compound 19-1) in THF was added. The reaction mixture was stirred at -78 °C for 5 min, allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with aqueous NH<sub>4</sub>Cl (10.0 mL)



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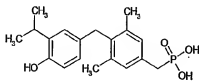
and extracted with ether (10 .0 mL). The organic layer was dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with 50% acetone in hexanes to afford dimethyl 2-[3,5-dibromo-4-(4'-methoxy-3'-isopropylphenoxy)phenyl]ethylphosphonate (0.09 g, 43%) as a colorless oil:  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.64 (s, 2H), 6.82 (d,  $J$  = 10.0 Hz, 1H), 6.75 (d,  $J$  = 4.2 Hz, 1H), 6.44 (dd,  $J$  = 2.8, 10.2 Hz, 1H), 3.79 (d,  $J$  = 2.8 Hz, 6H), 3.76 (s, 3H), 3.30 (m, 1H), 2.94 (m, 2H), 2.23 (m, 2H), 1.17 (d,  $J$  = 7.0 Hz, 6H); LC-MS  $m/z$  = 537 [ $\text{C}_{20}\text{H}_{25}\text{Br}_2\text{O}_5\text{P} + \text{H}$ ] $^+$ ; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = acetone-hexanes (1:1);  $R_f$  = 0.50.

Step b:

[0962] The title compound was prepared from dimethyl 2-[3,5-dibromo-4-(4'-methoxy-3'-isopropylphenoxy)phenyl]ethylphosphonate according to the procedure described for the synthesis of compound 4, step b: mp: 56-59 °C;  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.02 (s, 1H), 7.65 (s, 2H), 6.64 (m, 2H), 6.21 (dd,  $J$  = 2.8, 10.2 Hz, 1H), 3.14 (m, 1H), 2.79 (m, 2H), 1.87 (m, 2H), 1.11 (d,  $J$  = 7.0 Hz, 6H); LC-MS  $m/z$  = 495 [ $\text{C}_{17}\text{H}_{19}\text{Br}_2\text{O}_5\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{17}\text{H}_{19}\text{Br}_2\text{O}_5\text{P} + 0.5 \text{H}_2\text{O}$ ): C, 40.58; H, 4.01. Found: C, 40.26; H, 4.22.

### Example 68

**Compound 68:** [3,5-Dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)benzyl] phosphonic Acid



Step a:

[0963] To a solution of methyl 3,5-methyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)benzoate 1.80 g, 5.0 mmol, Example 47, step a) in THF (30.0 mL) at 0 °C was slowly added DIBAL (12.6 mL, 12.6 mmol). The

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reaction mixture was stirred at 0 °C for 2 h and quenched with potassium sodium tartrate. The reaction mixture was diluted with hexanes and stirred at room temperature for 2 h. The organic layer was separated, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was dissolved in ether (95.0 mL) and slowly added to a solution of carbon tetrabromide and  $\text{PPh}_3$  in ether (20.0 mL). The reaction mixture was stirred at room temperature for 16 h and filtered through a Celite plug. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel, eluting with 10% ethyl acetate in hexanes to afford 3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)benzyl bromide (1.82 g, 93%) as white solid:  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.13 (s, 2H), 6.93 (m, 2H), 6.67 (d,  $J = 7.2$  Hz, 1H), 5.17 (s, 2H), 4.54 (s, 2H), 4.02 (s, 2H), 3.48 (s, 3H), 3.31 (m, 1H), 2.25 (s, 6H), 1.17 (d,  $J = 7.0$  Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:9);  $R_f = 0.8$ .

## Step b:

[0964] To a solution of 3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)benzyl bromide (0.60 g, 1.53 mmol) in DMF (5.0 mL) at room temperature was slowly added a solution of trimethylphosphite (0.57 g, 4.60 mmol) in DMF (1.0 mL). The reaction mixture was stirred at 140 °C for 3 h and cooled to room temperature. The mixture was quenched with water (10 mL) and extracted with ethyl acetate (10 mL). The organic layer was dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with 50% acetone in hexanes to afford dimethyl 2-[3,5- dibromo-4-(4'-methoxymethoxy-3'-isopropylphenoxy)]benzylphosphonate (0.20 g, 31%) as colorless oil:  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.04 (d,  $J = 2.4$  Hz, 2H), 6.93 (m, 2H), 6.69 (d,  $J = 7.2$  Hz, 1H), 5.17 (s, 2H), 4.01 (s, 2H), 3.72 (d,  $J = 10.2$  Hz, 6H), 3.28 (m, 1H), 3.22 (d,  $J = 21.3$  Hz, 2H), 2.25 (s, 6H), 1.17 (d,  $J = 7.0$  Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = acetone-hexanes (1:1);  $R_f = 0.5$ .

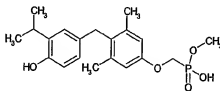
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Step c:

[0965] The title compound was prepared from dimethyl [3,5- dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)benzyl]phosphonate according to the procedure described for the synthesis of compound 7, step b: mp: 60-63;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.03 (s, 2H), 6.93 (m, 2H), 6.09(s, 1H), 6.58 (m, 2H), 3.95 (s, 2H), 3.23 (m, 1H), 3.08 (d,  $J = 21.0$  Hz, 2H), 2.24 (s, 6H), 1.17 (d,  $J = 7.0$  Hz, 6H); LC-MS  $m/z = 349$  [ $\text{C}_{19}\text{H}_{25}\text{O}_4\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{19}\text{H}_{25}\text{O}_4\text{P} + 0.6\text{H}_2\text{O}$ ): C, 63.47; H, 7.55. Found: C, 63.53; H, 7.35.

## Example 69

**Compound 69:** [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonic acid monomethyl ester



Step a:

[0966] A solution of [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonic acid (compound 7, 105 mg, 0.29 mmol), oxalyl chloride (0.5 mL) and DMF (2 drops) in dichloromethane was refluxed for 2 hours then concentrated under reduced pressure and azeotroped twice with dichloromethane. The residue was taken in dichloromethane and triethylamine (0.16 mL, 1.2 mmol) followed by methanol (1 mL) were added at rt. After stirring at rt for 2 hours, the reaction mixture was quenched with brine, diluted with ethyl acetate, washed with 1 N sodium hydroxide, then brine. The organics were dried over sodium sulfate, concentrated under reduced pressure and the residue purified by column chromatography (silica gel, dichloromethane/methanol 96/4 to 92/8) to give dimethyl [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonate (75 mg, 70%):  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  6.92 (d,  $J = 3.0$  Hz, 1H), 6.68 (s, 2H), 6.66 (d,  $J =$

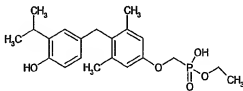
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9.0 Hz, 1H), 6.52 (dd,  $J = 9.0, 3.0$  Hz, 1H), 4.31 (d,  $J = 10.2$  Hz, 2H), 3.89 (d,  $J = 11.0$  Hz, 6H), 3.15 (heptuplet,  $J = 7.0$  Hz, 1H), 2.19 (s, 6H), 1.21 (d,  $J = 7.0$  Hz, 6H); TLC conditions: Merck silica gel, 250 microns; Mobile phase = dichloromethane-methanol (9:1);  $R_f = 0.65$ .

Step b:

[0967] A 1 N solution of sodium hydroxide (1 mL, 1 mmol) was added to a solution of dimethyl [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonate (75 mg, 0.19 mmol) in THF at rt. The biphasic solution was stirred at rt for 24 hours then diluted with ethyl acetate and extracted twice with 1 N sodium hydroxide. The combined aqueous extracts were acidified to pH 1 with concentrated hydrochloric acid and extracted twice with ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure to give the title compound (55 mg, 76%):  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  6.92 (d,  $J = 3.0$  Hz, 1H), 6.68 (s, 2H), 6.60-6.4 (m, 2H), 4.31 (d,  $J = 10.2$  Hz, 2H), 3.89 (d,  $J = 11.0$  Hz, 3H), 3.15 (heptuplet,  $J = 7.0$  Hz, 1H), 2.19 (s, 6H), 1.21 (d,  $J = 7.0$  Hz, 6H); LC-MS  $m/z = 379.4$  [ $\text{C}_{20}\text{H}_{27}\text{O}_3\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{20}\text{H}_{27}\text{O}_3\text{P} + 0.4 \text{H}_2\text{O}$ ): C, 62.30; H, 7.27. Found: C, 62.20; H, 7.51.

**Compound 69-1:** [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonic acid monoethyl ester



Step a:

[0968] Diethyl[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*propylbenzyl)phenoxy]methylphosphonate was prepared from diethyl [3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonate (Example 7, step a) according to the procedure described for the synthesis of compound 7-14, step a:  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.00 (s, 1H), 6.85

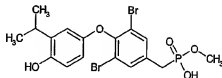
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(m, 1H), 6.74 (s, 2H), 6.63 (m, 1H), 6.48 (m, 1H), 4.36 (d,  $J = 9.0$  Hz, 2H), 4.13 (m, 4H), 3.81 (s, 2H), 3.14 (m, 1H), 2.18 (s, 6H), 1.27 (m, 6H), 1.12 (d,  $J = 6.0$  Hz, 6H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (1:4);  $R_f = 0.40$ .

## Step b:

[0969] The title compound was prepared according to the procedure described for the synthesis of compound 69, step b:  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  9.00 (s, 1H), 6.85 (m, 1H), 6.73 (s, 2H), 6.61 (m, 1H), 6.48 (m, 1H), 4.21 (d,  $J = 9.0$  Hz, 2H), 4.06 (m, 2H), 3.81 (s, 2H), 3.14 (m, 1H), 2.18 (s, 6H), 1.24 (m, 3H), 1.12 (d,  $J = 6.0$  Hz, 6H); LC-MS  $m/z = 393$  [ $\text{C}_{21}\text{H}_{29}\text{O}_5\text{P} - \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{21}\text{H}_{29}\text{O}_5\text{P} + 0.1 \text{ H}_2\text{O}$ ): C, 63.98; H, 7.47. Found: C, 63.93, H, 7.07. HPLC conditions: Column = Agilent zorbax RP18, 150 $\times$ 3.0 mm; Mobile phase = Solvent B (Acetonitrile) = HPLC grade acetonitrile; Solvent A (buffer) = 20 mM potassium phosphate buffer (pH 4.7). Flow rate = 0.75 mL/min; UV@ 254 nm.  $rt = 13.98$  min).

**Compound 69-2:** [3,5-dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)benzyl] phosphonic Acid Monomethyl Ester



## Step a:

[0970] To a solution of [3,5-dimethyl-4-(3'-isopropyl-4'-methoxyphenoxy)]benzyl bromide (intermediate for the synthesis of compound 19-1, 0.20 g, 0.40 mmol) in DMF (2.5 mL) at room temperature was slowly added a solution of trimethylphosphite (0.57 g, 4.60 mmol) in DMF (0.5 mL). The reaction mixture was stirred at 140 °C for 3 h and cooled to room temperature. The mixture was quenched with water (10 mL) and extracted with ethyl acetate (10 mL). The organic layer was dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product

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was purified by column chromatography on silica gel, eluting with 50% acetone in hexanes to afford dimethyl [3,5-dibromo-4-(3'-isopropyl-4'-methoxyphenoxy)benzyl]phosphonate (0.10 g, 49%) as colorless oil: <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.68 (s, 2H), 6.83 (d, *J* = 7.2 Hz, 1H), 6.72 (s, 1H), 6.45 (d, *J* = 7.2 Hz, 1H), 3.81 (s, 6H), 3.77 (s, 3H), 3.38 (d, *J* = 10.2 Hz, 2H), 3.28 (m, 1H), 1.17 (d, *J* = 7.0 Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = acetone-hexanes (1:1); R<sub>f</sub> = 0.5.

## Step b

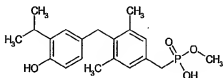
[0971] To a solution dimethyl [3,5- dibromo-4-(3'-isopropyl-4'-methoxyphenoxy)benzyl]phosphonate (0.22 g, 0.42 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) at -78 °C was slowly added BBr<sub>3</sub> (0.63 mL, 0.63 mmol). After 5 min, the reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was quenched with ice-water and extracted with ethyl acetate (10 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with 50% acetone in hexanes to afford dimethyl [3,5-dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)benzyl]phosphonate (0.06 g, 28%) as white solid: <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 9.07 (s, 1H), 7.67 (d, *J* = 2.2 Hz, 1H), 6.65 (m, 2H), 6.22 (dd, *J* = 2.8, 10.2 Hz, 1H), 3.64 (d, *J* = 11.0 Hz, 6H), 3.40 (d, *J* = 15.0, 2H), 3.18 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = acetone-hexanes (1:1); R<sub>f</sub> = 0.3.

## Step c

[0972] The title compound was prepared according to the procedure described for the synthesis of compound 69, step b: mp: 56-59 °C; <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 9.05 (s, 1H), 6.75 (s, 2H), 7.66 (d, *J* = 2.2 Hz, 1H), 6.66 (m, 2H), 6.22 (dd, *J* = 2.8, 10.2 Hz, 1H), 3.57 (d, *J* = 11.0 Hz, 3H), 3.12-3.23 (m, 3H), 1.10 (d, *J* = 7.0 Hz, 6H); LC-MS *m/z* = 495 [C<sub>17</sub>H<sub>19</sub> Br<sub>2</sub>O<sub>3</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>17</sub>H<sub>19</sub> Br<sub>2</sub>O<sub>3</sub>P): C, 41.32; H, 3.88. Found: C, 41.55; H, 4.02.

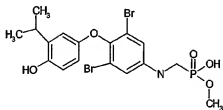
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**Compound 69-3:** [3,5-Dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)benzyl]phosphonic Acid Monomethyl ester



[0973] The title compound was prepared from dimethyl 2-[3,5- dibromo-4-(4'-methoxymethoxy-3'-isopropylphenoxy)]benzylphosphonate (compound 68, step b) according to the procedure described for the synthesis of compound 7-14, step a followed by compound 69, step b: mp: 72-75;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.01 (d,  $J = 2.1$  Hz, 2 H), 6.84 (d,  $J = 2.1$  Hz, 1 H), 6.54 (m, 2 H), 3.94 (s, 2 H), 3.65 (d,  $J = 10.8$  Hz, 3 H), 3.21 (m, 1 H), 3.09 (d,  $J = 21.0$  Hz, 2 H), 2.23 (s, 6 H), 1.13 (d,  $J = 7.0$  Hz, 6 H); LC-MS  $m/z = 361$  [ $\text{C}_{20}\text{H}_{27}\text{O}_4\text{P} - \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{20}\text{H}_{27}\text{O}_4\text{P} + 0.2\text{H}_2\text{O}$ ): C, 65.63; H, 7.55. Found: C, 65.70; H, 7.44.

**Compound 69-4:** [3,5-dibromo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenylamino] -methylphosphonic acid monomethyl ester



Step a:

[0974] To a stirring mixture of *t*-butyl [3,5-dibromo-4-(3'-isopropyl-4'-methoxymethoxyphenoxy)phenyl]carbamate (compound 84, step f, 0.15 g, 0.28 mmol) and acetonitrile (4.0 mL) was added  $\text{Cs}_2\text{CO}_3$  (0.179 g, 0.55 mmol) followed by dimethyl 4-chloro-benzenesulfonyloxymethylphosphonate (0.087 g, 0.28 mmol). The reaction mixture was stirred at 40 °C for 16 h and the solvent evaporated. The reaction mixture was partitioned with ethyl acetate and  $\text{H}_2\text{O}$ , the organic layer was concentrated and the crude was purified by preparatory thin-layer chromatography on silica gel, eluting with

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ethyl acetate-hexanes (3:2) to afford dimethyl *N*-*tert*-butoxycarbonyl-[3,5-dibromo-4-(3'-isopropyl-4'-methoxymethoxyphenoxy)phenylamino]methylphosphonate as an oil (0.040 g, 22%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.88 (s, 2 H), 7.03 (m, 1 H), 6.72 (m, 1 H), 6.46 (m, 1 H), 5.18 (s, 2 H), 4.25 (m, 2 H), 3.64 (d, *J* = 9.0 Hz, 6 H), 3.41 (s, 3 H), 3.27 (m, 1 H), 1.44 (s, 9 H), 1.15 (d, *J* = 6.0 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (4:1); R<sub>f</sub> = 0.42

## Step b:

[0975] To a mixture of *N*-*tert*-butoxycarbonyl-[3,5-dibromo-4-(3'-isopropyl-4'-methoxymethoxyphenoxy)phenylamino]methylphosphonate (0.27 g, 0.41 mmol) in methanol (6.0 mL) was added 3 N HCl (0.68 mL, 2.03 mmol). The reaction mixture was heated with microwave radiation at 100 °C in a sealed vial for 5 minutes. The solvent was removed and the residue was partitioned with ethyl acetate and water. The organic layer was coevaporated with methanol and concentrated under reduced pressure to afford *N*-*tert*-butoxycarbonyl-[3,5-dibromo-4-(4'-hydroxy-3'-isopropyl-phenoxy)phenylamino]methylphosphonate (0.075 g, 87%) as a solid: <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.90 (s, 1 H), 7.09 (s, 2 H), 6.65 (m, 2 H), 6.28 (m, 2 H), 3.70 (m, 6 H), 3.66 (m, 2 H), 3.19 (m, 1 H), 1.14 (d, *J* = 6.0 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (4:1); R<sub>f</sub> = 0.25

## Step c:

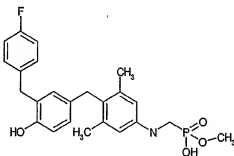
[0976] To a stirred solution of *N*-*tert*-butoxycarbonyl-[3,5-dibromo-4-(4'-hydroxy-3'-isopropyl-phenoxy)phenylamino]methylphosphonate (0.075 g, 0.14 mmol) in THF (2.0 mL) was added 1 M NaOH (0.70 mL, 0.86 mmol). The reaction mixture was stirred at rt for 16 h, then heated at 40 °C for 5 hrs. The reaction mixture was cooled to 0 °C, treated 2 N HCl (pH ~ 1), diluted with ethyl acetate and H<sub>2</sub>O, partitioned, and the organic layer was extracted with H<sub>2</sub>O. The organic layer was filtered and concentrated to afford the title compound as a grey solid (0.070 g, 96%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ



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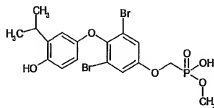
8.97 (s, 1 H), 7.07 (s, 2 H), 6.65 (m, 2 H), 6.25 (m, 1 H), 3.64 (m, 2 H), 3.42 (s, 3 H), 3.16 (m, 1 H), 1.14 (d,  $J = 6.0$  Hz, 6 H); LC-MS  $m/z = 510$  [ $C_{17}H_{20}Br_2NO_3P - H$ ] $^+$ ; HPLC conditions: Column = Shimadzu LC-A8, SPD-10A; YMC Pack RP-18 filter, 150×4.6; Mobile phase = Solvent A Acetonitrile/0.05% TFA; Solvent B =  $H_2O$ /0.05% TFA. Flow rate = 2.0 mL/min; UV@ 254 nm. Retention time in minutes. (rt = 8.81/20.00, 93% purity).

**Compound 69-5:** [(3,5-Dimethyl-4-[3'-(4-fluorobenzyl)-4'-hydroxybenzyl]-phenylamino)methyl]methylphosphonic acid monomethyl ester



[0977] Prepared from benzyl *N*-[3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl)phenyl]carbamate (compound 79, step b) according to the procedure described for the synthesis of compound 69-4:  $^1H$  NMR (300 MHz,  $DMSO-d_6$ ):  $\delta$  9.15 (s, 1 H), 7.01 – 7.22 (m, 4 H), 6.76 (s, 1 H), 6.67 (d,  $J = 8.1$  Hz, 1 H), 6.58 (d,  $J = 8.1$  Hz, 1 H), 6.40 (s, 2 H), 3.79 (s, 2 H), 3.71 (s, 2 H), 3.58 (d,  $J = 10.5$  Hz, 3 H), 3.29 (m, 2 H), 2.07 (s, 6 H); LC-MS  $m/z = 444$  [ $C_{24}H_{27}FNO_4P + H$ ] $^+$ ; Anal Calcd for ( $C_{24}H_{27}FNO_4P + 2.2H_2O$ ): C, 59.67; H, 6.55; N, 2.90. Found: C, 59.40; H, 6.24; N, 3.31.

**Compound 69-6:** [3,5-dibromo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)-phenoxy]methylphosphonic acid monomethylester



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Step a:

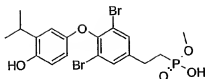
[0978] To a stirring mixture of DMF (20.0 mL) and NaH (0.074 g, 1.86 mmol) at 0 °C was added 3,5-dibromo-4-(3-isopropyl-4-hydroxy-phenoxy)phenol (Intermediate for the synthesis of compound 8-1, 0.75 g, 1.86 mmol) dissolved in DMF (2.0 mL). The reaction mixture was allowed to stir at rt for 1 hr and cooled to 0 °C. Dimethyl 4-chlorobenzenesulfonyloxymethylphosphonate (0.11 g, 0.36 mmol) was added and the reaction mixture was stirred at rt for 16 h. The reaction was quenched with ice H<sub>2</sub>O, the pH was adjusted to 1 with 2 M HCl, and the mixture was partitioned with ethyl acetate and H<sub>2</sub>O. The organic layer was concentrated and coevaporated with acetone (2X). The residue was treated with a hexane/ethyl acetate mixture and sonicated to afford dimethyl [3,5-dibromo-4-(4-hydroxy-3-*iso*-propyl-phenoxy)phenoxy]methylphosphonate as a white solid precipitate (0.070 g, 34%): <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 9.00 (s, 1H), 7.47 (s, 2H), 6.65 (m, 2H), 6.23 (m, 1H), 4.60 (d, *J* = 10.0 Hz, 2H), 3.75 (d, *J* = 10.0 Hz, 6H), 3.12 (m, 1H), 1.09 (d, *J* = 6.0 Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate; R<sub>f</sub> = 0.60

Step b:

[0979] To a stirred solution of dimethyl [3,5-dibromo-4-(4-hydroxy-3-*iso*-propyl-phenoxy)phenoxy]methylphosphonate (0.155 g, 0.30 mmol) in THF (4.0 mL) was added 2 M NaOH (0.89 mL, 1.77 mmol). The reaction mixture was stirred at rt for 48 h, cooled to 0 °C, treated with conc. HCl (pH ~ 1), and partitioned with ethyl acetate and H<sub>2</sub>O. The organic layer was extracted with H<sub>2</sub>O (1X). The organic layer was concentrated, dissolved in acetone, filtered and concentrated to afford the title compound as an off-white solid (0.110 g, 73%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.03 (s, 1H), 7.47 (s, 2H), 6.66 (m, 2H), 6.27 (m, 1H), 4.41 (d, *J* = 9.0 Hz, 2H), 3.69 (d, *J* = 9.0 Hz, 3H), 3.17 (m, 1H), 1.14 (d, *J* = 6.0 Hz, 6H); LC-MS *m/z* = 510 [C<sub>17</sub>H<sub>19</sub>Br<sub>2</sub>O<sub>6</sub>P-H]<sup>+</sup>.

**Compound 69-7:** 2-[3,5-Dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)-phenyl]ethylphosphonic Acid Monomethyl Ester

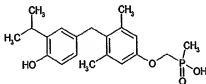
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[0980] The title compound was prepared from dimethyl-2-[3,5-dibromo-4-(4'-methoxy-3'-isopropylphenoxy)phenyl]ethylphosphonate (Example 67) according to the procedures described for the synthesis of Example 69-2. MP: 65-68 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.62 (s, 2H), 6.65 (m, 2H), 6.34 (dd,  $J = 11.2, 2.1$  Hz, 1H), 3.73 (d,  $J = 10.5$  Hz, 1H), 3.25 (m, 1H), 2.95 (m, 2H), 2.16 (m, 2H), 1.18 (d,  $J = 7.0$  Hz, 6H); LC-MS  $m/z = 509$  [ $\text{C}_{18}\text{H}_{21}\text{Br}_2\text{O}_3\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{18}\text{H}_{21}\text{Br}_2\text{O}_3\text{P}$ ): C, 42.55; H, 4.17. Found: C, 42.72; H, 3.90.

### Example 70

**Compound 70:** [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonic acid



Step a:

[0981] Solid sodium hydroxide (400 mg, 10 mmol) was added to a solution of diethyl[3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonate (compound 7, step a, 500 mg, 1.08 mmol) in THF (6 mL) and water (2 mL). The biphasic mixture was stirred at rt for 2 days, then diluted with ethyl acetate and washed with brine then 1 N hydrochloric acid, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. The crude material was carried over without purification:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.96 (d,  $J = 2.1$  Hz, 1H), 6.91 (d,  $J = 8.1$  Hz, 1H), 6.71 (s, 2H), 6.66 (dd,  $J = 8.1, 2.1$  Hz, 1H), 5.12 (s, 2H), 4.4-4.2 (m, 4H), 3.94 (s, 2H), 3.51 (s, 3H), 3.31 (heptuplet,  $J = 7.0$  Hz, 1H), 2.23 (s, 6H), 1.41 (t,  $J = 7.0$  Hz, 3H), 1.21 (d,  $J = 7.0$  Hz, 6H).

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Step b:

[0982] Thionyl chloride (120  $\mu$ L, 1.62 mmol) was added to a solution of crude [3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenoxy] methylphosphonic acid monoethyl ester (1.08 mmol) and pyridine (510  $\mu$ L, 6.48 mmol) in dichloromethane at rt. After stirring at rt for 18 hours, the yellow solution was concentrated under reduced pressure. The yellow oil was dissolved in THF (10 mL) and the solution cooled to -78 °C. A solution of MeMgBr in THF (3M, 1.1 mL, 3.3 mmol) was added to the solution of chloridate at -78 °C. After stirring at -78 °C for 15 min, the reaction mixture was quenched at -78 °C with acetic acid (324  $\mu$ L, 5.4 mmol), diluted with ethyl acetate and washed successively with saturated solution of sodium bicarbonate, a 10% solution of copper sulfate, brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, ethyl acetate/methanol 99/1 to 95/5) to give ethyl [3,5-dimethyl-4-(4'-methoxymethoxy-3'-*iso*-propylbenzyl)phenoxy]methyl methylphosphinate (318 mg, 68%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.98 (s, 1H), 6.92 (d,  $J$  = 8.4 Hz, 1H), 6.70 (s, 2H), 6.66 (d,  $J$  = 8.4 Hz, 1H), 5.19 (s, 2H), 4.4-4.2 (m, 4H), 3.96 (s, 2H), 3.51 (s, 3H), 3.33 (heptuplet,  $J$  = 7.0 Hz, 1H), 2.26 (s, 6H), 1.68 (d,  $J$  = 15 Hz, 3H), 1.4 (t,  $J$  = 7.0 Hz, 3H), 1.22 (d,  $J$  = 7.0 Hz, 6H); TLC conditions: Merck silica gel, 250 microns; Mobile phase = dichloromethane-methanol (9:1);  $R_f$  = 0.5.

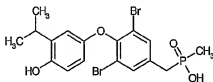
Step c:

[0983] The title compound was prepared according to the procedure described for the synthesis of compound 7, step b, (225.8 mg):  $^1\text{H}$  NMR (300 MHz, DMSO  $d_6$ )  $\delta$  9.00 (s, 1H), 6.86 (d,  $J$  = 1.8 Hz, 1H), 6.73 (s, 2H), 6.63 (d,  $J$  = 8.4 Hz, 2H), 6.46 (dd,  $J$  = 8.4, 1.8 Hz, 1H), 4.11 (d,  $J$  = 8.4 Hz, 4H), 3.82 (s, 2H), 3.51 (s, 3H), 3.14 (heptuplet,  $J$  = 7.0 Hz, 1H), 2.19 (s, 6H), 1.43 (d,  $J$  = 14.7 Hz, 3H), 1.12 (d,  $J$  = 7.0 Hz, 6H); LC-MS  $m/z$  = 363.1 [ $\text{C}_{20}\text{H}_{27}\text{O}_4\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{20}\text{H}_{27}\text{O}_4\text{P} + 0.2 \text{H}_2\text{O}$ ): C, 65.63; H, 7.55. Found: C, 65.47; H, 7.57.

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## Example 71

**Compound 71:** [3,5-Dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)benzyl] methylphosphinic Acid



## Step a:

[0984] To a solution of 3,5-dibromo-4-(3'-isopropyl-4'-methoxyphenoxy)benzyl bromide (intermediate for the synthesis of compound 19-1, 0.30 g, 0.60 mmol) in DMF (4.0 mL) at room temperature was slowly added a solution of diethyl methylphosphonite (0.25 g, 1.8 mmol) in DMF (0.5 mL). The reaction mixture was stirred at 100 °C for 3 h and cooled to room temperature. The mixture was quenched with water (10 mL) and extracted with ethyl acetate (10 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with 50% acetone in hexanes to afford ethyl [3,5-dibromo-4-(3'-isopropyl-4'-methoxyphenoxy)benzyl]methylphosphinate (0.29 g, 92%) as a colorless oil: <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 7.69 (d, *J* = 2.8 Hz, 1H), 6.84 (d, *J* = 10 Hz, 1H), 6.73 (d, *J* = 4.2 Hz, 1H), 6.40 (dd, *J* = 2.8, 10.2 Hz, 1H), 3.98 (m, 2H), 3.73 (s, 3H), 3.20 (m, 1H), 1.38 (d, *J* = 10.2 Hz, 3H), 1.19 (t, *J* = 7.8 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 6H); LC-MS *m/z* = 521 [C<sub>20</sub>H<sub>25</sub> Br<sub>2</sub>O<sub>4</sub>P + H]<sup>+</sup>; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = acetone-hexanes (1:1); R<sub>f</sub> = 0.50.

## Step b:

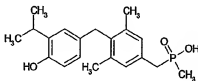
[0985] The title compound was prepared according to the procedure described for the synthesis of compound 4, step b: mp: 61-63 °C; <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 9.05 (s, 1H), 7.65 (d, *J* = 2.4 Hz, 2H), 6.67 (m, 2H), 6.23 (dd, *J* = 2.8, 10.2 Hz, 1H), 3.36 (d, *J* = 10.2 Hz, 3H), 3.14 (m, 1H), 1.28 (d, *J* = 10.2

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Hz, 3H), 1.11 (d,  $J = 7.0$  Hz, 6H); LC-MS  $m/z = 479$  [ $C_{17}H_{19}Br_2O_4P + H$ ]<sup>+</sup>;  
 Anal. Calcd for ( $C_{17}H_{19}Br_2O_4P$ ): C, 42.71; H, 4.01. Found: C, 42.45; H, 4.40.

### Example 72

**Compound 72:** [3,5-Dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)benzyl]methylphosphinic Acid



Step a:

[0986] To a solution of [3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)]benzyl bromide (compound 68, step a, 0.25 g, 0.64 mmol) in DMF (4.0 mL) at room temperature was slowly added a solution of diethyl methylphosphite (0.26 g, 1.92 mmol) in DMF (1.0 mL). The reaction mixture was stirred at 110 °C for 2 h and cooled to room temperature. The mixture was quenched with water (10 mL) and extracted with ethyl acetate (10 mL). The organic layer was dried over  $MgSO_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with 80% acetone in hexanes to afford ethyl [3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)benzyl]methylphosphinate (0.18 g, 70%) as colorless oil:  $^1H$  NMR (300 MHz,  $CD_3OD$ ):  $\delta$  7.04 (d,  $J = 2.4$  Hz, 2H), 6.91 (m, 2H), 6.72 (d,  $J = 7.2$  Hz, 1H), 5.18 (s, 2H), 4.07 (m, 2H), 4.01 (s, 2H), 3.47 (s, 3H), 3.28 (m, 1H), 3.22 (d,  $J = 21.3$  Hz, 2H), 2.25 (s, 6H), 1.45 (d,  $J = 14.1$  Hz, 3H), 1.17 (d,  $J = 7.0$  Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = acetone-hexanes (1:1);  $R_f = 0.3$ .

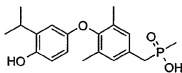
Step b:

[0987] The title compound was prepared according to the procedure described for the synthesis of compound 7, step b: mp: 170-173;  $^1H$  NMR (300 MHz,

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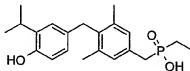
CD<sub>3</sub>OD):  $\delta$  6.97 (s, 2H), 6.79 (s, 1H), 6.52 (m, 2H), 3.91 (s, 2H), 3.20 (m, 1H), 3.09 (d,  $J = 17.7$  Hz, 2H), 2.20 (s, 6H), 1.37 (d,  $J = 14.1$  Hz, 3H), 1.10 (d,  $J = 7.0$  Hz, 6H); LC-MS  $m/z = 347$  [C<sub>20</sub>H<sub>27</sub>O<sub>3</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>20</sub>H<sub>27</sub>O<sub>3</sub>P + 0.3 H<sub>2</sub>O): C, 68.28; H, 7.91. Found: C, 68.33; H, 9.11.

**Compound 72-2:** [3,5-Dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)-benzyl]-methylphosphinic Acid



[0988] The title compound was prepared from intermediate 4-(4-methoxy-3-isopropylphenoxy)-3,5-dimethylbenzyl bromide (example 19-3) according to the procedures described for the synthesis of Example 72. MP: 58-61 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD):  $\delta$  7.08 (d,  $J = 2.1$  Hz, 2H), 6.62 (m, 2H), 6.30 (m, 1H), 3.25 (m, 1H), 3.14 (d,  $J = 21.0$  Hz, 2H), 2.11 (s, 6H), 1.40 (d,  $J = 14.1$  Hz, 2H), 1.16 (d,  $J = 7.0$  Hz, 6H); LC-MS  $m/z = 349$  [C<sub>19</sub>H<sub>25</sub>O<sub>4</sub>P + H]<sup>+</sup>. Anal. Calcd for (C<sub>19</sub>H<sub>25</sub>O<sub>4</sub>P + 0.7H<sub>2</sub>O): C, 63.22; H, 7.37. Found: C, 62.90; H, 6.92.

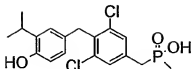
**Compound 72-3:** [3,5-Dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-ethylphosphinic Acid



[0989] The title compound was prepared from diethyl ethylphosphite according to the procedure described for the synthesis of Example 72. MP: 78-81 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD):  $\delta$  7.02 (d,  $J = 2.1$  Hz, 2H), 6.83 (d,  $J = 2.1$  Hz, 1H), 6.58 (m, 2H), 3.96 (s, 2H), 3.25 (m, 1H), 3.14 (d,  $J = 21.0$  Hz, 2H), 2.25 (s, 6H), 1.69 (m, 2H), 1.40 (d,  $J = 14.1$  Hz, 2H), 1.15 (m, 3H), 1.14 (d,  $J = 7.0$  Hz, 6H); LC-MS  $m/z = 361$  [C<sub>21</sub>H<sub>29</sub>O<sub>3</sub>P + H]<sup>+</sup>. Anal. Calcd for (C<sub>21</sub>H<sub>29</sub>O<sub>3</sub>P + 0.2H<sub>2</sub>O): C, 69.29; H, 8.14. Found: C, 69.20; H, 8.05.

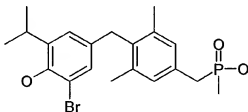
**Compound 72-4:** [3,5-dichloro-4-(4'-hydroxy-3'-iso-propylbenzyl)benzyl]-methylphosphinic acid

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[0990] The title compound was prepared from 3,5-dichloro-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)phenol (intermediate for the synthesis of example 7-5) according to the procedures used for the synthesis of example 94 steps a-b, example 68 step a and example 72. MP: 160-163 °C;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  9.12 (s, 1H), 7.40 (s, 2H), 7.00 (s, 1H), 6.70 (m, 2H), 4.11 (s, 2H), 3.15-3.10 (m, 1H) 3.12 (d,  $J$  = 18.0 Hz, 2H), 1.29 (d,  $J$  = 15.0 Hz, 3H), 1.12 (d,  $J$  = 4.5 Hz, 6H); Anal. Calcd for ( $\text{C}_{18}\text{H}_{21}\text{Cl}_2\text{O}_3\text{P}$ ): C, 55.83; H, 5.47. Found: C, 55.87; H, 5.61. LC-MS  $m/z$  = 387 [ $\text{C}_{18}\text{H}_{21}\text{Cl}_2\text{O}_3\text{P-H}$ ] $^+$ ; HPLC conditions: Column = Kromasil; C18-100 $\times$ 4.6 mm; Mobile phase = Solvent A: MeOH; Solvent B:  $\text{H}_2\text{O}$ /0.05% TFA. Flow rate = 1.0 mL/min; UV@ 254 nm. Retention time in minutes. (rt = 13.76/25.00, 100% purity).

**Compound 72-5:** [4-(3-Bromo-4-hydroxy-5-isopropyl-benzyl)-3,5-dimethylbenzyl]-methyl-phosphinic acid



Step a:

[0991] [3,5-Dimethyl-4-(5'-bromo-4'-hydroxy-3'-isopropylbenzyl)benzyl]-methylphosphinic acid ethyl ester (example 72 step a) was prepared according to the procedure described for the synthesis of compound 7-14, step b.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.02 (d,  $J$  = 2.4 Hz, 2H), 6.80 (s, 1H), 6.81 (s, 1H), 4.08 (m, 2H), 4.0 (s, 2H), 3.34 (m, 1H), 3.18 (d,  $J$  = 17.7 Hz, 2H), 2.25 (s, 6H), 1.50 (d,  $J$  = 14.1 Hz, 3H), 1.20 (m, 6H), 1.13 (m, 6H).



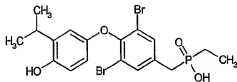
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Step b:

[0992] The title compound was prepared according to the procedure described for the synthesis of compound 7, step b: MP: 96-98;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  8.68 (s, 1H), 6.96 (s, 1H), 6.91 (s, 1H), 6.73 (s, 1H), 3.91 (s, 2H), 3.20 (m, 1H), 2.98 (d,  $J = 17.7$  Hz, 2H), 2.17 (s, 6H), 1.18 (d,  $J = 14.1$  Hz, 3H), 1.10 (d,  $J = 7.0$  Hz, 6H); LC-MS  $m/z = 426$  [ $\text{C}_{20}\text{H}_{26}\text{BrO}_3\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{20}\text{H}_{27}\text{O}_3\text{P} + 0.5 \text{ H}_2\text{O}$ ): C, 55.31; H, 6.27. Found: C, 55.02; H, 6.00. HPLC conditions: Column = Waters Atlantis; dC18-150 $\times$ 4.6 mm; Mobile phase = Solvent A:  $\text{H}_2\text{O}/0.05\%$  TFA; Solvent B: ACN/ $0.05\%$  TFA. Flow rate = 2.0 mL/min; UV@ 254 nm. Retention time in minutes. (rt = 8.50/20.00, 98% purity).

## Example 73

**Compound 73:** [3,5-Dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)benzyl] ethylphosphonic Acid



Step a:

[0993] To a solution of 3,5-dibromo-4-(3'-isopropyl-4'-methoxyphenoxy)benzyl bromide (intermediate for the synthesis of compound 19-1, 0.19 g, 0.39 mmol) in DMF (3.0 mL) at room temperature was slowly added a solution of diethyl ethylphosphite (0.17 g, 1.17 mmol) in DMF. The reaction mixture was stirred at 100 °C for 2 h and cooled to room temperature. The mixture was quenched with water (10 mL) and extracted with ethyl acetate (10 mL). The organic layer was dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with 50% acetone in hexanes to afford diethyl [3,5-dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)benzyl]

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ethylphosphinate (0.19 g, 93%) as colorless oil:  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.70 (d,  $J = 2.8$  Hz, 2H), 6.84 (d,  $J = 10$  Hz, 1H), 6.71 (d,  $J = 4.2$  Hz, 1H), 6.48 (dd,  $J = 2.8, 10.2$  Hz, 1H), 4.09 (m, 2H), 3.81 (s, 3H), 3.30 (m, 3H), 1.84 (m, 2H), 1.13-1.40 (m, 12H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = acetone-hexanes (1:1);  $R_f = 0.50$ .

Step b:

[0994] The title compound was prepared according to the procedure described for the synthesis of compound 4, step b: mp: 80-83 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.68 (d,  $J = 2.8$  Hz, 2H), 6.64 (m, 2H), 6.36 (dd,  $J = 2.8, 10.2$  Hz, 1H), 3.33 (m, 1H), 3.24 (d,  $J = 15.6$  Hz, 2H), 1.76 (m, 2H), 1.19 (m, 9H); LC-MS  $m/z = 493$  [ $\text{C}_{18}\text{H}_{21}\text{Br}_2\text{O}_4\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{18}\text{H}_{21}\text{Br}_2\text{O}_4\text{P}$ ): C, 43.93; H, 4.30. Found: C, 43.56; H, 4.26.

### Example 74

**Compound 74:** ethyl [(4-methylphenyl)sulfonyloxymethyl]methylphosphinate

Step a:

[0995] To a stirred solution of diethyl (4-methylphenyl)sulfonyloxymethylphosphonate (intermediate for the synthesis of compound 7, 2.00 g, 6.21 mmol) in benzene (20.0 mL) was added phosphorous pentachloride (1.55 mL, 7.45 mmol) and the reaction mixture was refluxed until homogenous, then stirred at rt overnight. The solvents were removed and the residue was coevaporated with toluene (2X). The crude was used as is in the next step.

Step b:

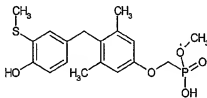
[0996] To the crude ethyl (4-methylphenyl)sulfonyloxymethylphosphinate monochloridate (2.00 g, 6.39 mmol) in dry THF (30.0 mL) at -78 °C was added MeMgBr (2.20 mL, 6.97 mmol, 3.0 M in diethyl ether). The reaction was quenched immediately after the MeMgBr addition with 1 mL of acetic

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acid. The reaction mixture was diluted with ethyl acetate and H<sub>2</sub>O and the organic layer was washed twice with saturated aqueous NaHCO<sub>3</sub> and once with H<sub>2</sub>O. The organic layer was concentrated and coevaporated with MeOH. The product was obtained by precipitation from hexanes to afford the title compound as a white solid (1.40 g, 77% over two steps): <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 7.85 (m, 2H), 7.52 (m, 2H), 4.30 (d, *J* = 12.0 Hz, 2H), 3.90 (m, 2H), 2.40 (s, 3H), 1.45 (d, *J* = 21.0 Hz, 3H), 1.15 (m, 3H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-methanol (9:1); R<sub>f</sub> = 0.27.

### Example 75

**Compound 75:** [3,5-Dimethyl-4-(4'-hydroxy-3'-methylsulfanylbenzyl)phenoxy]methylphosphonic acid monomethyl ester



#### Step a:

[0997] To a stirring solution of triisopropyl-[3,5-dimethyl-4-(4'-methoxymethoxybenzyl)phenoxy]silane (1.2 g, 2.8 mmol) and TMEDA (0.51 mL, 3.42 mmol) in ether (25 mL) at -20 °C was added *n*-BuLi (1.37 mL, 2.5 M in hexanes). The mixture was stirred at -20 °C for 1 h and methyldisulfanylmethane (0.5 mL, 5.6 mmol) was added. The reaction mixture was stirred at -20 °C for 1 h, allowed to warm to room temperature and stirred for 4 h. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl and diluted with diethyl ether. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford triisopropyl-[3,5-dimethyl-4-(4'-methoxymethoxy-3'-methylsulfanylbenzyl)phenoxy]silane as a yellow oil (1.3 g, 98%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 6.95 (d, *J* = 8.1 Hz, 1H), 6.78 (d, *J* = 2.1 Hz, 1H), 6.4 (dd, *J* = 2.1, 8.1 Hz, 1H), 6.60 (s, 2H),

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5.19 (s, 2H), 3.90 (s, 2H), 3.35 (s, 3H), 2.27 (s, 3H), 2.14 (s, 6H), 1.25 (m, 3H), 1.09 (d,  $J = 6.9$  Hz, 18H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 15% ethyl acetate in hexanes;  $R_f = 0.46$ .

Step b:

[0998] To a stirring solution of triisopropyl-[3,5-dimethyl-4-(4'-methoxymethoxy-3'-methylsulfanylbenzyl)phenoxy]silane (1.3 g, 2.74 mmol) in THF (20 mL) at room temperature was added tetrabutylammonium fluoride (3.4 mL, 1.0 M in THF). The reaction mixture was stirred at room temperature for 2 h, diluted with diethyl ether and washed with water (30 mLx2). The solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (4:6) to afford 3,5-dimethyl-4-(4'-methoxymethoxy-3'-methylsulfanylbenzyl)phenol as a white solid (0.75 g, 86%):  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  9.04 (s, 1H), 6.93 (d,  $J = 8.4$  Hz 1H), 6.86 (d,  $J = 1.2$  Hz 1H), 6.61 (dd,  $J = 1.2, 8.4$  Hz, 1H), 6.49 (s, 2H), 5.19 (s, 2H), 3.86 (s, 2H), 3.40 (s, 3H), 2.32 (s, 3H), 2.12 (s, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 30% ethyl acetate in hexanes;  $R_f = 0.45$ .

Step c:

[0999] To a solution of 3,5-dimethyl-4-(4'-methoxymethoxy-3'-methylsulfanylbenzyl)phenol (0.54 g, 1.7 mmol) in  $\text{CH}_3\text{CN}$  (20 mL) at room temperature was added  $\text{Cs}_2\text{CO}_3$  (0.82 g, 2.54 mmol) and dimethyl (4-chlorophenylsulfonyloxy)methylphosphonate (0.54 g, 1.7 mmol). The reaction mixture was refluxed for 16 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and saturated  $\text{NaHCO}_3$ . The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (4:1) to afford dimethyl [3,5-dimethyl-4-(4'-methoxymethoxy-3'-methylsulfanylbenzyl)phenoxy]methylphosphonate as a colorless oil (0.3 g, 40%):  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  6.89 (m, 2H), 6.75 (s, 2H), 6.58 (m,

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1H), 5.16 (s, 2H), 4.42 (d,  $J = 10.0$  Hz, 2H), 3.89 (s, 2H), 3.73 (d,  $J = 10.6$  Hz, 6H), 3.37 (s, 3H), 2.30 (s, 3H), 2.17 (s, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 80% ethyl acetate in hexanes;  $R_f = 0.31$ .

Step d:

[1000] To a stirring solution of dimethyl [3,5-dimethyl-4-(4'-methoxymethoxy-3'-methylsulfanylbenzyl)phenoxy]methylphosphonate (0.051 g, 0.12 mmol) in MeOH (1.5 mL) at room temperature was added HCl (0.93 mL, 1 N), and heated at 100 °C for 5 min by microwave. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and sat. NaHCO<sub>3</sub>. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate to afford dimethyl[3,5-dimethyl-4-(4'-hydroxy-3-methylsulfanylbenzyl)phenoxy]methylphosphonate as a colorless oil (0.037 g, 80%): <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 9.57 (s, 1H), δ 6.74 (m, 3H), 6.63 (d,  $J = 8.0$  Hz, 1H), 6.49 (m, 1H), 4.42 (d,  $J = 9.8$  Hz, 2H), 3.83 (s, 2H), 3.72 (d,  $J = 10.3$  Hz, 6H), 2.26 (s, 3H), 2.16 (s, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate;  $R_f = 0.45$ .

Step e:

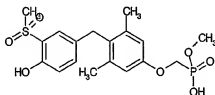
[1001] To a stirring solution of dimethyl [3,5-dimethyl-4-(4'-hydroxy-3-methylsulfanylbenzyl)phenoxy]methylphosphonate (0.037 g, 0.093 mmol) in THF (3 mL) at room temperature was added NaOH (0.37 mL, 1 N), and stirred for 48 h at room temperature. It was acidified by 1 N HCl to pH = 2, and the mixture was partitioned between EtOAc and sat. NaHCO<sub>3</sub>. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford the title compound as a light brown foam (0.030g, 84%): <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 9.61 (s, 1H), 6.78 (s, 1H), 6.64 (m, 3H), 6.46 (d,  $J = 8.0$  Hz, 1H), 3.96 (d,  $J = 9.2$  Hz, 2H), 3.81 (s, 2H), 3.51 (d,  $J = 9.8$  Hz, 3H), 2.26 (s, 3H), 2.14 (s, 6H); LC-MS  $m/z = 383$  [C<sub>18</sub>H<sub>23</sub>O<sub>5</sub>PS + H]<sup>+</sup>; Anal

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Calcd for  $(C_{18}H_{23}O_3PS + 0.1H_2O + 0.4CH_2Cl_2)$ : C, 52.85; H, 5.78. Found: C, 52.68; H, 5.45.

### Example 76

**Compound 76:** [3,5-Dimethyl-4-(4'-hydroxy-3'-methanesulfonylbenzyl)-phenoxy]methylphosphonic acid monomethyl ester



Step a:

[1002] To a stirring solution of dimethyl [3,5-dimethyl-4-(4'-methoxymethoxy-3'-methylsulfonylbenzyl)phenoxy]methylphosphonate (compound 75, step c, 0.25 g, 0.57 mmol) in  $CH_2Cl_2$  (15 mL) at room temperature was added m-CPBA (0.34 g, 2 mmol). The mixture was stirred for 16 h at room temperature, quenched with saturated  $Na_2SO_3$  and diluted with  $CH_2Cl_2$ . The organic layer was collected and dried over  $Na_2SO_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate to afford dimethyl [3,5-dimethyl-4-(3'-methanesulfonyl-4'-methoxymethoxybenzyl)phenoxy]methylphosphonate as a colorless oil (0.14 g, 53%):  $^1H$  NMR (200 MHz,  $DMSO-d_6$ ):  $\delta$  7.43 (s, 1H), 7.25 (s, 2H), 6.77 (s, 2H), 5.35 (s, 2H), 4.43 (d,  $J = 10.0$  Hz, 2H), 3.95 (s, 2H), 3.73 (d,  $J = 10.6$  Hz, 6H), 3.41 (s, 3H), 3.25 (s, 3H), 2.17 (s, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate;  $R_f = 0.31$ .

Step b:

[1003] To a stirring solution of dimethyl [3,5-dimethyl-4-(3'-methanesulfonyl-4'-methoxymethoxybenzyl)phenoxy]methylphosphonate (0.14 g, 0.3 mmol) in MeOH (2 mL) at room temperature was added HCl (0.3

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mL, 10 N), and heated at 100 °C for 5 min by microwave. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and sat. NaHCO<sub>3</sub>. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with methanol-ethyl acetate (5:95) to afford dimethyl [3,5-dimethyl-4-(4'-hydroxy-3'-methanesulfonylbenzyl)phenoxy]methylphosphonate as a colorless oil (0.042 g, 33%): <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 10.87 (s, 1H), 7.30 (d, *J* = 1.8 Hz, 1H), 7.13 (dd, *J* = 1.8, 8.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.76 (s, 2H), 4.42 (d, *J* = 10.0 Hz, 2 Hz), 3.89 (s, 2H), 3.74 (d, *J* = 10.6 Hz, 6H), 3.19 (s, 3H), 2.16 (s, 6H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = 5% methanol in ethyl acetate; R<sub>f</sub> = 0.42.

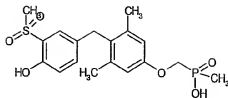
Step c:

[1004] To a stirring solution of dimethyl [3,5-dimethyl-4-(4'-hydroxy-3'-methanesulfonylbenzyl)phenoxy]methylphosphonate (0.042 g, 0.098 mmol) in THF (3 mL) at room temperature was added NaOH (0.39 mL, 1 N), and stirred for 48 h at room temperature. It was acidified by 1 N HCl to pH = 2, and the mixture was partitioned between EtOAc and sat. NaHCO<sub>3</sub>. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford the title compound as a light yellow foam (0.016g, 39%): <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 10.96 (s, 1H), 7.34 (d, *J* = 1.8 Hz, 1H), 7.11 (dd, *J* = 1.8, 8.4 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.71 (s, 2H), 4.07 (d, *J* = 9.6 Hz, 2H), 3.88 (s, 2H), 3.58 (d, *J* = 10.4 Hz, 3H), 3.19 (s, 3H), 2.15 (s, 6H); LC-MS *m/z* = 415 [C<sub>18</sub>H<sub>23</sub>O<sub>7</sub>PS + H]<sup>+</sup>; Anal Calcd for (C<sub>18</sub>H<sub>23</sub>O<sub>7</sub>PS + 1.1H<sub>2</sub>O): C, 49.79; H, 5.86. Found: C, 49.47; H, 5.73.

### Example 77

**Compound 77:** [(3,5-dimethyl-4-(4-hydroxy-3-methanesulfonylbenzyl)phenoxy)methyl]methylphosphinic acid

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Step a:

[1005] To a solution of 3,5-dimethyl-4-(4'-methoxymethoxy-3'-methylsulfanylbenzyl)phenol (compound 75, step b, 0.11 g, 0.35 mmol) in CH<sub>3</sub>CN (5 mL) at room temperature was added Cs<sub>2</sub>CO<sub>3</sub> (0.17 g, 0.52 mmol) and ethyl [(4-methylphenyl)sulfonyloxymethyl]methylphosphinate (compound 74, 0.1 g, 0.35 mmol). The reaction mixture was refluxed for 16 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and saturated NaHCO<sub>3</sub>. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate to afford ethyl [(3,5-dimethyl-4-(4'-methoxymethoxy-3'-methylsulfanylbenzyl)phenoxy)methyl]methylphosphinate as a colorless oil (0.3 g, 91%): <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 6.89 (m, 2H), 6.76 (s, 2H), 6.56 (dd, *J* = 1.8, 8.4 Hz, 1H), 5.16 (s, 2H), 4.27 (m, 2H), 4.04 (m, 2H), 3.89 (s, 2H), 3.37 (s, 3H), 2.30 (s, 3H), 2.17 (s, 6H), 1.51 (d, *J* = 14.6 Hz, 3H), 1.23 (t, *J* = 7.0 Hz, 3H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate; R<sub>f</sub> = 0.32.

Step b:

[1006] To a stirring solution of ethyl [(3,5-dimethyl-4-(4'-methoxymethoxy-3'-methylsulfanylbenzyl)phenoxy)methyl]methylphosphinate (0.14 g, 0.32 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at room temperature was added m-CPBA (0.19 g, 1.12 mmol). The mixture was stirred for 16 h at room temperature, quenched with saturated Na<sub>2</sub>SO<sub>3</sub> and diluted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was collected and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate to afford ethyl [(3,5-dimethyl-4-(3'-



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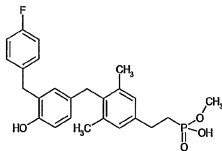
methanesulfonyl-4'-methoxymethoxybenzyl)phenoxy)methyl]  
methylphosphinate as a colorless oil (0.07 g, 47%):  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  7.42 (s, 1H), 7.25 (s, 2H), 6.78 (s, 2H), 5.35 (s, 2H), 4.27 (m, 2H), 4.04 (m, 2H), 3.95 (s, 2H), 3.41 (s, 3H), 3.25 (s, 3H), 2.17 (s, 6H), 1.51 (d,  $J = 14.6$  Hz, 3H), 1.23 (t,  $J = 7.0$  Hz, 3H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 5% methanol in ethyl acetate;  $R_f = 0.32$ .

### Step c:

[1007] To a stirring solution of ethyl [(3,5-dimethyl-4-(3'-methanesulfonyl-4'-methoxymethoxybenzyl)phenoxy)methyl]methylphosphinate (0.07 g, 0.15 mmol) in  $\text{CH}_2\text{Cl}_2$  (6 mL) at  $-20^\circ\text{C}$  was added TMSBr (0.2 mL, 1.5 mmol). The mixture was stirred for 16 h at room temperature and concentrated under reduced pressure. The residue was added MeOH and stirred for 1 h at room temperature. The solution was concentrated under reduced pressure to afford the title compound as a light pink foam (0.04 g, 67%):  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  10.84 (s, 1H), 7.31 (d,  $J = 1.8$  Hz, 1H), 7.17 (dd,  $J = 1.8, 8.4$  Hz, 1H), 6.95 (d,  $J = 8.4$  Hz, 1H), 6.74 (s, 2H), 4.08 (d,  $J = 8.4$  Hz, 2H), 3.89 (s, 2H), 3.19 (s, 3H), 2.16 (s, 6H), 1.39 (d,  $J = 14.6$  Hz, 3H); LC-MS  $m/z = 399$  [ $\text{C}_{18}\text{H}_{23}\text{O}_6\text{PS} + \text{H}$ ] $^+$ ; Anal Calcd for ( $\text{C}_{18}\text{H}_{23}\text{O}_6\text{PS} + 0.2\text{CH}_2\text{Cl}_2 + 1.8\text{H}_2\text{O}$ ): C, 48.81; H, 6.08. Found: C, 48.52; H, 6.22.

### Example 78

**Compound 78:** 2-[3,5-Dimethyl-4-(3'-(4-fluorobenzyl)-4'-hydroxybenzyl)phenyl]ethylphosphonic acid monomethyl ester



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Step a:

- [1008] To a solution of 4-bromophenol (13.84 gm, 0.08 Mol), 4-fluorobenzyl alcohol (8.68 gm, 0.08 Mol), and 120 mL of dichloroethane was added zinc bromide (21 gm, 0.09 Mol). The reaction mixture was stirred at 60 °C for 24 h, filtered and concentrated under reduced pressure. Pure product was obtained by flash chromatography using SiO<sub>2</sub>, dichloromethane/hexane [1:1] as eluant to give 4-bromo-2-(4-fluorobenzyl)phenol (9.25 g, 41%) as colorless oil: <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 9.79 (s, 1H), 7.16 (m, 5H), 6.74 (d, *J* = 8.8 Hz, 1H), 3.82 (s, 2H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = methylene chloride-hexanes (1:1); R<sub>f</sub> = 0.38.

Step b:

- [1009] To a stirring solution of 4-bromo-2-(4-fluorobenzyl)phenol (16 g, 59.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) at room temperature was added ethyl-diisopropylamine (15.6 mL, 89.85 mmol) and chloro-methoxy-methyl ether (6.1 mL, 79.67 mmol). After stirring at reflux for 16 h, water was added and the mixture was partitioned with ethyl acetate. The organic layer was collected and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:9) to afford 4-bromo-2-(4-fluorobenzyl)methoxymethoxybenzene as a light yellow oil (16.4 g, 88%): <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): 6.96 – 7.40 (m, 7H), 5.20 (s, 2H), 3.89 (s, 2H), 3.26 (s, 3H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 6% ethyl acetate in hexanes; R<sub>f</sub> = 0.79.

Step c:

- [1010] To a stirring solution of 4-bromo-2-(4-fluorobenzyl)methoxymethoxybenzene (6.2 g, 19.93 mmol) in THF (80 mL) at –78 °C was added *n*-BuLi (8.8 mL, 2.5 M in hexanes). The mixture was stirred at –78 °C for 1 h and 2,6-dimethyl-4-trisopropylsilyloxy-benzaldehyde (6.11 g, 19.93 mmol) was added. The reaction mixture was stirred at –78 °C for 1 h, allowed to warm to room temperature and stirred for 1 h. The reaction mixture

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was quenched with saturated  $\text{NH}_4\text{Cl}$  and diluted with diethyl ether. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:9) to afford (2,6-dimethyl-4-triisopropylsilyloxyphenyl)-[3-(4-fluorobenzyl)-4-methoxymethoxyphenyl]methanol as a light yellow oil (8.3 g, 75%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  6.88 – 7.20 (m, 7H), 6.47 (s, 2H), 5.97 (d,  $J = 4.0$  Hz, 1H), 5.65 (d,  $J = 4.0$  Hz, 1H), 5.14 (s, 2H), 3.85 (s, 2H), 3.25 (s, 3H), 2.11 (s, 6H), 1.24 (m, 3H), 1.08 (d,  $J = 7.2$  Hz, 18H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 10% ethyl acetate in hexanes;  $R_f = 0.47$ .

Step d:

[1011] To a stirring solution of (2,6-dimethyl-4-triisopropylsilyloxyphenyl)-[3-(4-fluorobenzyl)-4-methoxymethoxyphenyl]methanol (8.3 g, 15.01 mmol) in  $\text{CH}_2\text{Cl}_2$  (150 mL) at room temperature was added  $\text{Et}_3\text{SiH}$  (9.6 mL, 60.04 mmol) and TFA (4.5 mL, 60.04 mmol). The reaction mixture was stirred at room temperature for 6 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and saturated  $\text{NaHCO}_3$ . The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. Then to this stirring solution of crude product in  $\text{CH}_2\text{Cl}_2$  (150 mL) at room temperature was added ethyl-diisopropyl-amine (2.6 mL, 15.01 mmol) and chloro-methoxy-methyl ether (1 mL, 13.51 mmol). The mixture was refluxed for 16 h, added water. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:9) to afford [3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl)phenoxy]triisopropylsilane as a light yellow oil (7 g, 87%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  6.66 – 7.19 (m, 7H), 6.54 (s, 2H), 5.12 (s, 2H), 3.82 (s, 4H), 3.25 (s, 3H), 2.11 (s, 6H), 1.23 (m, 3H), 1.06 (d,  $J = 7.2$  Hz, 18H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:9);  $R_f = 0.68$ .

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Step e:

[1012] To a stirring solution of [3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl)phenoxy]triisopropylsilane (7 g, 13.04 mmol) in THF (100 mL) at room temperature was added tetrabutylammonium fluoride (16.3 mL, 1.0 M in THF). The reaction mixture was stirred at room temperature for 2 h, diluted with diethyl ether and washed with water (30 mLx2). The solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (3:7) to afford 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]phenol as a colorless oil (4.6 g, 93%):  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  6.99 (s, 1H),  $\delta$  7.13 (m, 4H), 6.85 (m, 2H), 6.67 (m, 1H), 6.43 (s, 2H), 5.12 (s, 2H), 3.84 (s, 2H), 3.76 (s, 2H), 3.24 (s, 3H), 2.07 (s, 6H), TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (15:85);  $R_f$  = 0.45.

Step f:

[1013] To a solution of 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]phenol (4.6 g, 12.09 mmol) and DMAP (4.4 g, 36.27 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) at 0 °C was slowly added trifluoromethanesulfonyl anhydride (3.1 mL, 18.14 mmol). The reaction mixture was stirred at 0 °C for 2 h and quenched with water (60 mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (15:85) to afford 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]phenyl trifluoromethanesulfonate as a colorless oil (5.8 g, 94%):  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  6.91 – 7.28 (m, 7H), 6.80 (s, 1H), 6.69 (d,  $J$  = 8.4 Hz, 1H), 5.15 (s, 2H), 3.91 (s, 2H), 3.84 (s, 2H), 3.25 (s, 3H), 2.22 (s, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (15:85);  $R_f$  = 0.65.

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## Step g:

- [1014] To a solution of 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]phenyl trifluoromethanesulfonate (5.8 g, 11.32 mmol) in DMF (80 mL) in a bomb apparatus was added MeOH (9.2 mL, 226.4 mmol), Pd(OAc)<sub>2</sub> (0.25 g, 1.13 mmol), DPPP (0.47 g, 1.13 mmol) and TEA (3.2 mL, 22.64 mmol). 60 psi of CO was then infused and the reaction mixture was stirred at 90 °C for 16 h. The bomb was cooled to 0 °C, vented, its content poured into cold 1 N HCl and extracted with EtOAc twice. The combined EtOAc extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (15:85) to afford methyl 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]benzoate as a colorless oil (4.8 g, 100%): <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 7.64 (s, 2H), 6.68 – 7.25 (m, 7H), 5.13 (s, 2H), 3.97 (s, 2H), 3.83 (s, 5H), 3.24 (s, 3H), 2.23 (s, 6H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (15:75); R<sub>f</sub> = 0.52.

## Step h:

- [1015] To a stirring solution of dimethyl methylphosphonate (1.44 mL, 13.26 mmol) in THF (60 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes, 5.3 mL), the reaction mixture was stirred at –78 °C for 1 h, then 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]benzoate (1.4 g, 3.31 mmol) in THF (10 mL) was added at the same temperature. The reaction mixture was stirred at –78 °C for 1.5 h, then at room temperature for 1 h. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl and diluted with diethyl ether. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate to afford dimethyl [2-(3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl)phenyl)-2-oxo-ethyl]phosphonate as a light yellow oil (1.53 g, 90%): <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 7.70 (s, 2H), 6.66 – 7.22 (m, 7H), 5.14 (s, 2H), 3.97 (s, 2H), 3.84 (s, 2H), 3.82 (d, *J* = 22.4 Hz, 2H), 3.65 (d, *J* = 11.0 Hz, 6H), 3.24 (s, 3H), 2.25 (s, 6H). TLC

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conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (4:1);  $R_f = 0.35$ .

Step i:

- [1016] To a stirring solution of dimethyl [2-(3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl)phenyl)-2-oxo-ethyl]phosphonate (1.34 g, 2.6 mmol) in MeOH (60 mL) at 0 °C was added  $\text{NaBH}_4$  (0.49 g, 13.02 mmol). The reaction mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to afford crude dimethyl [2-(3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl)phenyl)-2-hydroxy-ethyl]phosphonate as a light yellow oil (1.4 g, 100%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.11 (m, 6H), 6.89 (m, 2H), 6.67 (m, 1H), 5.44 (d,  $J = 4.2$  Hz, 1H), 5.12 (s, 2H), 4.80 (m, 1H), 3.87 (s, 2H), 3.84 (s, 2H), 3.55 (m, 8H), 3.22 (s, 3H), 2.17 (s, 6H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate;  $R_f = 0.41$ .

Step j:

- [1017] To a stirring solution of [2-(3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl)phenyl)-2-hydroxy-ethyl]phosphonate (1.4 g, 2.7 mmol) in  $\text{CH}_2\text{Cl}_2$  (80 mL) at room temperature in EtOAc (20 mL) and AcOH (2 mL) was added Pd/C (0.2 g), and the reaction mixture was stirred under 50 PSI  $\text{H}_2$  at room temperature for 16 h. The mixture was filtered through a celite plug. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate to afford dimethyl 2-[3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl)phenyl]ethylphosphonate as a colorless oil (0.37 g, 27%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  6.81 – 7.22 (m, 8H), 6.69 (m, 1H), 5.12 (s, 2H), 3.84 (s, 4H), 3.62 (d,  $J = 10.6$  Hz, 6H), 3.24 (s, 3H), 2.65 (m, 2H), 2.14 (s, 6H), 2.02 (m, 2H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate;  $R_f = 0.49$ .

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## Step k:

[1018] To a stirring solution of dimethyl 2-[3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl)phenyl]ethylphosphonate (0.32 g, 0.64 mmol) in MeOH (4 mL) at room temperature was added HCl (2.1 mL, 3 N), and heated at 100 °C for 5 min by microwave. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and sat. NaHCO<sub>3</sub>. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate to afford dimethyl 2-[3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-hydroxybenzyl)phenyl]ethylphosphonate as a colorless oil (0.27 g, 92%): <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 9.19 (s, 1H), 6.98 – 7.22 (m, 4H), 6.89 (s, 2H), 6.63 (m, 3H), 3.79 (s, 2H), 3.76 (s, 2H), 3.62 (d, *J* = 10.8 Hz, 6H), 2.65 (m, 2H), 2.13 (s, 6H), 2.02 (m, 2H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate; R<sub>f</sub> = 0.44.

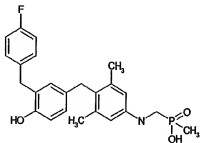
## Step l:

[1019] To a stirring solution of dimethyl 2-[3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-hydroxybenzyl)phenyl]ethylphosphonate (0.27 g, 0.59 mmol) in THF (10 mL) at room temperature was added NaOH (2.4 mL, 1 N), and the reaction mixture was brought to reflux. After 48 h, 1 N HCl was added to pH = 2, and the mixture was partitioned between EtOAc and sat. NaHCO<sub>3</sub>. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford the title compound as a light yellow solid (0.2 g, 77%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): 9.18 (s, 1H), 6.88 – 7.22 (m, 4H), 6.86 (s, 2H), 6.71 (d, *J* = 2.1 Hz, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.55 (dd, *J* = 2.1, 8.1 Hz, 1H), 3.78 (s, 2H), 3.76 (s, 2H), 3.52 (d, *J* = 11.1 Hz, 3H), 2.65 (m, 2H), 2.11 (s, 6H), 1.84 (m, 2H); mp: 125 – 127 °C; LC-MS *m/z* = 443 [C<sub>25</sub>H<sub>28</sub>FO<sub>4</sub>P + H]<sup>+</sup>; Anal Calcd for (C<sub>25</sub>H<sub>28</sub>FO<sub>4</sub>P + 0.5H<sub>2</sub>O): C, 66.51; H, 6.47. Found: C, 66.23; H, 6.61.

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## Example 79

**Compound 79:** [(3,5-Dimethyl-4-[3'-(4-fluorobenzyl)-4'-hydroxybenzyl]-phenylamino)methyl]methylphosphinic acid



## Step a:

[1020] To a stirring solution of afford methyl 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]benzoate (compound 78, step f, 2.8 g, 6.63 mmol) in MeOH (80 mL) at 0 °C was added NaOH (27 mL, 1 N). After heating at 50 °C for 16 h, the solvent was removed under reduced pressure and the residue was acidified with 1 N HCl to pH = 1, and the mixture was extracted with EtOAc. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]benzoic acid as white solid (2.7 g, 100%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): 12.71 (s, 1H), 7.64 (s, 2H), 7.01 - 7.22 (m, 4H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 2.1 Hz, 1H), 6.73 (dd, *J* = 2.1, 8.4 Hz, 1H), 5.15 (s, 2H), 3.98 (s, 2H), 3.86 (s, 2H), 3.27 (s, 3H), 2.25 (s, 6H).

## Step b

[1021] To a solution of 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]benzoic acid (2.3 g, 5.63 mmol) in toluene (80 mL) was added diphenylphosphoryl azide (1.22 mL, 5.63 mmol), triethylamine (1.57 mL, 11.26 mmol) and BnOH (2.9 mL, 28.15 mmol) at room temperature. The mixture was refluxed for 16 h. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and



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sat.  $\text{NH}_4\text{Cl}$ . The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:1) to afford benzyl *N*-[3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl)phenyl]carbamate as a yellow oil (2.9 g, 100%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.59 (s, 1H), 7.01- 7.44 (m, 11H), 6.92 (d,  $J$  = 8.7 Hz, 1H), 6.86 (d,  $J$  = 1.8 Hz, 1H), 6.76 (dd,  $J$  = 1.8, 8.7 Hz, 1H), 5.15 (s, 2H), 5.14 (s, 2H), 3.87 (s, 2H), 3.85 (s, 2H), 3.27 (s, 3H), 2.14 (s, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 15% ethyl acetate in hexanes;  $R_f$  = 0.55.

## Step c:

[1022] To a solution of benzyl *N*-[3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl)phenyl]carbamate (0.62 g, 1.21 mmol) in  $\text{CH}_3\text{CN}$  (10 mL) at room temperature was added  $\text{Cs}_2\text{CO}_3$  (0.79 g, 2.42 mmol) and ethyl [(4-methylphenyl)sulfonyloxymethyl]methylphosphinate (compound 74, 0.35 g, 1.21 mmol). The reaction mixture was refluxed for 16 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and saturated  $\text{NaHCO}_3$ . The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate to afford ethyl [(*N*-benzyloxycarbonyl-3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl)phenylamino)methyl]methylphosphinate as a colorless oil (0.065 g, 8.5%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.01- 7.44 (m, 11H), 6.92 (d,  $J$  = 8.4 Hz, 1H), 6.89 (d,  $J$  = 2.1 Hz, 1H), 6.73 (dd,  $J$  = 2.1, 8.4 Hz, 1H), 5.15 (s, 2H), 5.14 (s, 2H), 4.08 (d,  $J$  = 6.9 Hz, 2H), 3.91 (s, 2H), 3.85 (m, 3H), 3.63 (m, 1H), 3.27 (s, 3H), 2.18 (s, 6H), 1.32 (d,  $J$  = 14.4 Hz, 3H), 1.01 (t,  $J$  = 7.0 Hz, 3H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (4:1);  $R_f$  = 0.39.

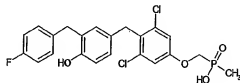
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Step d:

[1023] To a solution of ethyl [(*N*-benzyloxycarbonyl-3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl)phenylamino)methyl] methylphosphinate (0.065 g, 0.1 mmol) in EtOH (30 mL) at room temperature was added Pd/C (0.04 g) and the reaction mixture was stirred under 50 PSI H<sub>2</sub> at room temperature for 16 h. The mixture was filtered through a Celite plug. The solvent was removed under reduced pressure and the residue (0.045 g, 0.09 mmol) was dissolved into CH<sub>2</sub>Cl<sub>2</sub> (8 mL). TMSBr (0.12 mL, 0.9 mmol) was then added at - 20 °C. The reaction mixture was stirred at room temperature for 16 h and concentrated under reduced pressure. MeOH was added to the residue and the solution was stirred at room temperature. After 1h, the solution was concentrated under reduced pressure and purified by Prep. LC-MS to afford the title compound as a white solid (0.014 g, 36%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.15 (s, 1H), 7.01 – 7.22 (m, 4H), 6.77 (d, *J* = 2.1 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.59 (dd, *J* = 2.1, 8.1 Hz, 1H), 6.41 (s, 2H), 3.79 (s, 2H), 3.71 (s, 2H), 3.25 (d, *J* = 10.2 Hz, 2H), 2.16 (s, 6H), 1.37 (d, *J* = 14.1 Hz, 3H); LC-MS *m/z* = 428 [C<sub>24</sub>H<sub>27</sub>FNO<sub>3</sub>P + H]<sup>+</sup>; Anal Calcd for (C<sub>24</sub>H<sub>27</sub>FNO<sub>3</sub>P + 1.6H<sub>2</sub>O): C, 63.18; H, 6.67; N, 3.07. Found: C, 62.87; H, 6.50; N, 2.96.

## Example 80

**Compound 80:** [(3,5-Dichloro-4-(3'-(4-fluorobenzyl)-4'-hydroxybenzyl)phenoxy)methyl]methylphosphonic acid



Step a:

[1024] 4-[(4-Benzyloxy-2,6-dichlorophenyl)[3-(4-fluorobenzyl)-4-methoxyphenoxy)methyl]methanol was prepared from 2,6-dichloro-4-

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benzyloxybenzaldehyde (*Organic Letters* 4:2833 (2002)) according to the procedure described for the synthesis of compound 78, step c. (0.58 gm, 20%); <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 7.38 (m, 5H), 7.13 (m, 7H), 6.95 (s, 2H), 6.32 (d, *J* = 4.8 Hz, 1H), 5.97 (d, *J* = 4.4 Hz, 1H), 5.15 (s, 4H), 3.88 (s, 2H), 3.26 (s, 3H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (3:1); R<sub>f</sub> = 0.45.

Step b:

- [1025] 5-Benzyloxy-1,3-dichloro-2-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]benzene was synthesized by combining (1.21 gm, 2.48 mmol) starting material, with dichloromethane 30 mL, TFA (0.92 mL, 12.4 mmol), and triethylsilane (2 mL, 12.4 mmol). The reaction was stirred at r.t for 1.5 h in an ice/water bath, poured into dichloromethane 50 mL, washed 1 x with 50 mL NaHCO<sub>3</sub>, 1 x with 25 mL H<sub>2</sub>O, 1 x with 25 mL HCl. The organics were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. (1.172 gm, 100 %); NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.37 (m, 5H), 7.15 (m, 4H), 7.08 (m, 4H), 6.94 (m, 2H), 5.14 (s, 4H), 4.06 (s, 2H), 3.85 (s, 2H), 3.25 (s, 3H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (3:1); R<sub>f</sub> = 0.40.

Step c:

- [1026] 3,5-Dichloro-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]phenol was prepared according to the procedure described for the synthesis of compound 35, step c. (0.183 gm, 40%); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 10.27 (bs, 1H), 7.23 (m, 4H), 7.10 (m, 4H), 6.86 (m, 2H), 6.84 (m, 3H), 5.14 (s, 2H), 4.02 (s, 2H), 3.85 (s, 2H), 3.25 (s, 3H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (3:1); R<sub>f</sub> = 0.32.

Step d:

- [1027] To a solution of 3,5-dichloro-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]phenol (0.08 gm, 0.19 mmol), acetonitrile (3 mL),

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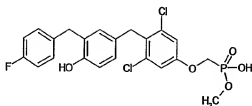
ethyl [(4-methylphenyl)sulfonyloxymethyl]methylphosphinate (compound 74, 0.105 gm, 0.38 mmol), was added cesium carbonate (0.153 gm, 0.47 mmol). The reaction was heated at reflux for 2 hours, then stirred over night at r.t. The reaction was filter into 25 ml ethyl acetate, washed 1 x with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. Ethyl [(3,5-dichloro-4-(3-(4-fluorobenzyl)-4-hydroxybenzyl)phenoxy)methyl]methylphosphinate was obtained by prep plate TLC using a 2mm x 20 x 20 cm  $\text{SiO}_2$  plate eluted with ethyl acetate. (0.06gm, 60%);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.23 (s, 2H), 7.17 (m, 2H), 7.07 (t,  $J = 8.7$  Hz, 2H), 6.95 (m, 2H), 6.86 (m, 1H), 5.14 (s, 2H), 4.41 (m, 2H), 4.07 (s, 2H), 4.04 (m, 2H), 3.86 (s, 2H), 3.25 (s, 3H);  $^{31}\text{P}$  NMR (121.4 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  46.13; TLC conditions: Uniplat silica gel, 250 microns; ethyl acetate;  $R_f = 0.22$ .

Step e:

[1028] Title compound was prepared according to the procedure described for the synthesis of compound 7, step b (0.032gm, 62%);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.27 (s, 1H), 7.18 (m, 4H), 7.06 (t,  $J = 8.7$  Hz, 2H), 6.84 (d,  $J = 1.8$  Hz, 1H), 6.71 (m, 2H), 4.20 (d,  $J = 8.1$  Hz, 2H), 4.01 (s, 2H), 3.78 (s, 2H), 1.39 (d,  $J = 14.7$  Hz, 3 H); TLC conditions: Uniplat silica gel, 250 microns; isopropanol/AcOH/ $\text{H}_2\text{O}$  [7:2:1];  $R_f = 0.65$ ; LC-MS  $m/z = 467$  [ $\text{C}_{22}\text{H}_{20}\text{Cl}_2\text{FO}_4\text{P} + \text{H}$ ]; Anal Calcd for ( $\text{C}_{22}\text{H}_{20}\text{Cl}_2\text{FO}_4\text{P} + 0.1 \text{ H}_2\text{O}$ ): C, 56.09; H, 4.32. Found: C, 55.94; H, 4.15.

### Example 81:

**Compound 81:** [3,5-Dichloro-4-(3'-(4-fluorobenzyl)-4'-hydroxybenzyl)phenoxy]methyl phosphonic acid monomethyl ester



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Step a:

[1029] Dimethyl[3,5-dichloro-4-(3'-(4-fluorobenzyl)-4'-methoxymethylbenzyl)phenoxy]methylphosphonate was prepared from 3,5-dichloro-4-[3'-(4-fluorobenzyl)-4'-hydroxybenzyl]phenol according to the procedure described for the synthesis of compound 75, step b (0.091 gm, 69%); <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 7.26 (s, 2H), 7.10 (m, 2H), 6.92 (m, 5H), 5.10 (s, 2H), 4.25 (d, *J* = 10.6 Hz, 2H), 4.07 (s, 2H), 3.85 (s, 3H), 3.74 (d, *J* = 11 Hz, 2H), 3.25 (s, 3H); TLC conditions: Uniplat silica gel, 250 microns; ethyl acetate-hexane [3:1]; R<sub>f</sub> = 0.32.

Step b

[1030] Dimethyl[3,5-dichloro-4-(3'-(4-fluorobenzyl)-4'-hydroxybenzyl)phenoxy]methylphosphonate was prepared according to the procedure described for the synthesis of compound 7-14, step a (0.093 gm, 81%); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.27 (s, 1H), 7.18 (m, 4H), 7.06 (t, *J* = 9 Hz, 2H), 6.84 (s, 1H), 6.69 (m, 2H), 4.57 (d, *J* = 10 Hz, 2H), 4.02 (s, 2H), 3.78 (s, 2H), 3.73 (d, *J* = 11 Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; ethyl acetate-hexane [3:1]; R<sub>f</sub> = 0.23.

Step c:

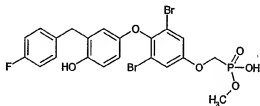
[1031] A solution of dimethyl [3,5-dichloro-4-(3'-(4-fluorobenzyl)-4'-hydroxybenzyl)phenoxy]methyl phosphonate (compound 80, step , 0.093 gm, 0.18 mmol), THF (3mL), and 1 N NaOH (0.75 mL) was heated at reflux for 12 h. The reaction was allowed to cool, concentrated under reduced pressure and diluted to a volume of 20 mL with H<sub>2</sub>O. The liquor was washed with 2 x with 10 mL of ethyl acetate, then acidified using conc. HCl to pH 3. The acidic solution was extracted with 2 x 10 mL of diethyl ether. The ether was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford the title compound (0.063 gm, 72%); <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 9.28 (s, 1H), 7.10 (m, 4H), 6.85 (s, 1H), 6.70 (s, 2H), 4.36 (d, *J* = 10 Hz, 2H), 4.01 (s, 2H), 3.77 (s, 2H), 3.64 (d, *J* = 10.5 Hz, 3H); TLC conditions: Uniplat silica gel, 250 microns; isopropanol/AcOH/H<sub>2</sub>O [7:2:1]; R<sub>f</sub> = 0.72; LC-MS

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$m/z$  485  $[C_{22}H_{20}Cl_2FO_3P + H]^+$ ; Anal Calcd for  $(C_{22}H_{20}Cl_2FO_3P)$ : C, 54.45; H, 4.15. Found: C, 54.45; H, 4.12.

### Example 82

**Compound 82:** [3,5-Dibromo-4-(3'-(4-fluorobenzyl)-4'-hydroxyphenoxy)methylphosphonic acid monomethyl ester.



Step a:

[1032] A mixture of 4-bromo-2-(4-fluorobenzyl)phenol (compound 78, step a, 6.0 gm, 21.4 mmol), 1.2 g of palladium on activated carbon (10%) and 100 mL of methanol in a glass reaction vessel was shaken at 50 psi  $H_2$  over night, filtered and concentrated under reduced pressure. The resulting light orange oil was dissolved in 180 mL dichloromethane and washed 1 x with  $NaHCO_3$  saturated solution. The organic was dried over  $Na_2SO_4$ , filtered and concentrated under reduced pressure to afford 2-(4-fluorobenzyl)phenol (4.52 gm, 100%):  $^1H$  NMR (200 MHz,  $DMSO-d_6$ ):  $\delta$  9.39 (s, 1H), 7.22 (m, 2H), 7.02 (m, 3H), 6.74 (m, 2H), 3.84 (s, 2H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = methylene chloride-hexanes (1:1);  $R_f$  = 0.32.

Step b:

[1033] A mixture of 2-(4-fluorobenzyl)phenol (4.51 gm, 22.41 mmol), DMF (60 mL), potassium carbonate (7.78 gm, 56.02 mmol) and methyl iodine (1.67 mL, 26.81 mmol) was stirred at rt for 16 h. The reaction was poured into 150 mL ethyl acetate, filtered, washed 3x with 50 mL  $H_2O$ , 1x with 100 mL brine, dried over  $Na_2SO_4$ , filtered and concentrated under reduced pressure to afford 2-(4-fluorobenzyl)anisole (4.27 gm, 88%);  $^1H$  NMR (200 MHz,  $DMSO-d_6$ ):  $\delta$

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7.11(m, 7H), 3.88(s, 2H), 3.76(s, 3H); TLC conditions: Uniplat silica gel, 250 microns; methylene chloride-hexanes (1:1);  $R_f = 0.64$ .

Step c:

[1034] Bis[3-(4-fluorobenzyl)-4-methoxy]iodonium tetrafluoroborate was prepared from 2-(4-fluorobenzyl)anisole using the procedure from (Yokoyama *et al. J. Med. Chem.* 38:695 (1995)). (5.49gm, 40%);  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.94 (m, 4H), 7.15 (m, 12H), 3.86 (s, 4H), 3.25 (s, 6H); TLC conditions: Uniplat silica gel, 250 microns; dichloromethane-methanol [10:1];  $R_f = 0.53$ .

Step d:

[1035] 3,5-Dibromo-4-[3'-(4-fluorobenzyl)-4'-methoxyphenoxy]phenyl benzoate was prepared from bis[3-(4-fluorobenzyl)-4-methoxy]iodonium tetrafluoroborate and 3-benzoyloxy-2,6-dibromophenol according to the procedure described for the synthesis of compound 4, step a (2.15gm, 63%);  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.13(dd,  $J = 6.8, 1 \text{ Hz}$ , 2 H z), 7.90(s, 2H), 7.75(d,  $J = 7.2 \text{ Hz}$ , 1H), 7.63(t,  $J = 7 \text{ Hz}$ , 2H), 7.19(m, 4H), 6.92(d,  $J = 8.8 \text{ Hz}$ , 1H), 6.76(d,  $J = 3 \text{ Hz}$ , 1H), 6.51(dd,  $J = 6, 2.2 \text{ Hz}$ , 1H), 3.87(s, 2H), 3.74(s, 3H); TLC conditions: Uniplat silica gel, 250 microns; hexane-acetone [20:1];  $R_f = 0.24$ .

Step e:

[1036] To a mixture of 3,5-dibromo-4-[3'-(4-fluorobenzyl)-4'-methoxyphenoxy]phenyl benzoate (2.14 gm, 3.75 mmol) in THF 60 mL was added 1 N NaOH 20 mL. The reaction was stirred at r.t overnight, then poured into 120 mL ethyl acetate. The aqueous layer was removed and the organic was washed 2 x with aqueous  $\text{NaHCO}_3$ , 1 x with 1 N HCl 30 mL. The ethyl acetate was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give 3,5-dibromo-4-[3'-(4-fluorobenzyl)-4'-methoxyphenoxy]phenol (1.68 gm, 93%);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  10.27 (s, 1H), 7.20 (m, 2H), 7.05 (m, 4H), 6.87 (d,  $J = 9 \text{ Hz}$ , 1H), 6.65 (d,  $J =$

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3.3 Hz, 1H), 6.46 (dd,  $J = 9$ , 3 Hz, 1H), 3.84 (s, 2H), 3.71 (s, 3H); TLC conditions: Uniplat silica gel, 250 microns; hexane-ethyl acetate [3:1];  $R_f = 0.65$ .

Step f:

[1037] To a stirred solution of 3,5-dibromo-4-[3'-(4-fluorobenzyl)-4'-methoxyphenoxy]phenol (1.66 gm, 3.44 mmol), dichloromethane 100mL, was added boron tribromide (8.6 mL, 8.60 mmol) in an ice / water bath. The reaction was stirred overnight under a nitrogen atmosphere. The reaction was diluted with ethyl acetate 60 mL, filtered and washed with water 2 x with 10 mL and brine 3 x 10 mL. The ethyl acetate was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. 3,5-Dibromo-4-[3'-(4-fluorobenzyl)-4'-hydroxyphenoxy]phenol (1.06 gm, 66%) was obtained by flash chromatography using  $\text{SiO}_2$  eluted with a step gradient of hexane-ethyl acetate[3:1] 2L and hexane-ethyl acetate [3:2];  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  10.24 (s, 1H), 9.14 (s, 1H), 7.22 (m, 2H), 7.08 (m, 4H), 6.69 (td,  $J = 8.7$  Hz, 1H), 6.54 (d,  $J = 3.3$  Hz, 1H), 6.55 (dd,  $J = 8.4$ , 3.3 Hz, 1H), 6.35 (dd,  $J = 9$ , 3 Hz, 1H), 3.80 (s, 2H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = methylene chloride-hexanes (1:1);  $R_f = 0.55$ .

Step g:

[1038] To a stirred solution of 3,5-dibromo-4-[3'-(4-fluorobenzyl)-4'-hydroxyphenoxy] phenol (0.237 gm, 0.51 mmol), DMF 8mL, cesium carbonate (0.824, 2.53 mmol) in an ice / water bath was added diethyl trifluoromethylsulfonyloxymethylphosphonate (0.122 gm, 0.41 mmol). The reaction was stir overnight under a nitrogen atmosphere. The reaction was diluted with ethyl acetate 60 mL, filtered and washed with water 2 x with 10 mL and brine 3 x 10 mL. The ethyl acetate was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. Diethyl [3,5-dibromo-4-(3'-(4-fluorobenzyl)-4'-hydroxyphenoxy)methylphosphonate (0.124 g, 39%) was obtained by prep plate TLC using a 2mm x 20 cm x 20 cm prep plate eluted with ethyl acetate;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.18 (s, 1H), 7.47 (s,



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2H), 7.22 (t,  $J = 5.7$  Hz, 2H), 7.07 (t,  $J = 9$  Hz, 2H), 6.70 (d,  $J = 8.7$  Hz, 1H), 6.55 (d,  $J = 3.3$  Hz, 1H), 6.35 (dd,  $J = 9$  Hz and  $J = 3$  Hz, 1H), 4.54 (d,  $J = 8.7$  Hz, 2H), 4.11 (q,  $J = 7.2$  Hz, 4H), 3.80 (s, 2H), 1.26 (t,  $J = 7.2$  Hz, 6H);  $^{31}\text{P}$  NMR (121 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  18.87 (s, 1 P); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate;  $R_f = 0.42$ .

Step h:

[1039] To a stirred solution of diethyl [3,5-dibromo-4-(3'-(4-fluorobenzyl)-4'-hydroxyphenoxy)phenoxy]methylphosphonate (0.134 g, 0.22 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) at 0 °C was added TMSBr (0.24 g, 0.2 mL). The reaction mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature. The reaction mixture was stirred at room temperature for 16 h and the solvent was removed under reduced pressure. The residue was co-evaporated 3 x 5 mL dichloromethane and 1 x 5 mL methanol to give [3,5-dibromo-4-(3'-(4-fluorobenzyl)-4'-hydroxyphenoxy)phenoxy]methylphosphonic acid as a white foam (0.124 g, 100%);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.35 (s, 2H), 7.23 (m, 2H), 7.06 (t,  $J = 9$  Hz, 2H), 6.70 (d,  $J = 8.4$  Hz, 1H), 6.58 (d,  $J = 3.3$  Hz, 1H), 6.32 (dd,  $J = 9$  Hz and  $J = 3$  Hz, 1H), 3.92 (d,  $J = 8.7$  Hz), 3.79 (s, 2H); LC-MS  $m/z = 561$  [ $\text{C}_{20}\text{H}_{16}\text{Br}_2\text{FO}_6\text{P}-\text{H}$ ].

Step i:

[1040] Dimethyl [3,5-dibromo-4-(3'-(4-fluorobenzyl)-4'-hydroxyphenoxy)phenoxy]methylphosphonate was prepared from [3,5-dibromo-4-(3'-(4-fluorobenzyl)-4'-hydroxyphenoxy)phenoxy]methylphosphonic acid according to the procedure described for the synthesis of compound 69, step a (0.089 gm, 66%);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.19 (s, 1H), 7.48 (s, 2H), 7.22 (m, 2H), 7.07 (t,  $J = 9$  Hz, 2H), 6.70 (d,  $J = 9$  Hz, 1H), 6.55 (dd,  $J = 3.3$  Hz, 1H), 6.34 (dd,  $J = 3$  Hz and  $J = 9$  Hz, 1H), 4.59 (d,  $J = 9.9$  Hz, 2H), 3.80 (s, 2H), 3.75 (d,  $J = 10.5$  Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate;  $R_f = 0.40$ .

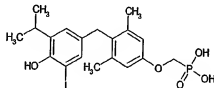
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Step j:

[1041] Title compound was prepared from dimethyl [3,5-dibromo-4-(3'-(4-fluorobenzyl)-4'-hydroxyphenoxy)phenoxy]methylphosphonate according to the procedure described for the synthesis of compound 81, step c (0.064 gm, 80%);  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.19 (s, 1H), 7.44 (s, 2H), 7.22 (t,  $J = 8$  Hz, 2H), 7.07 (t,  $J = 8$  Hz, 2H), 6.70 (d,  $J = 8.8$  Hz, 1H), 6.57 (d,  $J = 3$  Hz, 1H), 6.34 (dd,  $J = 8.8, 3$  Hz, 1H), 4.33 (d,  $J = 10$  Hz, 2H), 3.80 (s, 2H), 3.63 (d,  $J = 11$  Hz, 3H); TLC conditions: Uniplate silica gel, 250 microns; isopropanol/AcOH/ $\text{H}_2\text{O}$  [7:2:1];  $R_f = 0.74$ ; LC-MS  $m/z$  575 [ $\text{C}_{21}\text{H}_{18}\text{Br}_2\text{FO}_6\text{P} - \text{H}$ ]; Anal Calcd for ( $\text{C}_{21}\text{H}_{18}\text{Br}_2\text{FO}_6\text{P}$ ): C, 43.78; H, 3.15. Found: C, 43.66; H, 3.09.

## Example 83:

**Compound 83:** [3,5-dimethyl-4-(5'-iodo-4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonic acid



Step a:

[1042] Diethyl [3,5-dimethyl-4-(5'-iodo-4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonate was prepared from diethyl [3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenoxy]methylphosphonate (compound 69-1, step a) was prepared according to the procedure described for the synthesis of compound 13-15-*cis*:  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.06 (d,  $J = 2.4$  Hz, 1H), 6.89 (d,  $J = 2.4$  Hz, 1H), 6.77 (s, 2H), 4.42 (d,  $J = 11.2$  Hz, 2H), 4.28 (m, 4H), 3.93 (s, 2H), 3.28 (m, 1H), 2.24 (s, 6H), 1.40 (t,  $J = 7.2$  Hz, 6H), 1.17 (d,  $J = 7.0$  Hz, 6H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = acetone-hexanes (1:1);  $R_f = 0.6$ .

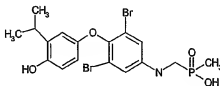
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Step b:

[1043] The title compound was prepared according to the procedure described for the synthesis of compound 7, step b: mp: 195-198 °C; 7.06 (d,  $J = 2.4$  Hz, 1H), 6.89 (d,  $J = 2.4$  Hz, 1H), 6.77 (s, 2H), 4.24 (d,  $J = 11.2$  Hz, 2H), 3.92 (s, 2H), 3.25 (m, 1H), 2.23 (s, 6H), 1.17 (d,  $J = 7.0$  Hz, 6H); LC-MS  $m/z = 491$  [ $C_{19}H_{24}IO_3P + H$ ]<sup>+</sup>; Anal. Calcd for ( $C_{19}H_{24}IO_3P$ ): C, 46.55; H, 4.93. Found: C, 46.66; H, 5.26.

## Example 84

**Compound 84:** [(3,5-dibromo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenylamino)methyl]methylphosphinic acid



Step a:

[1044] To a stirred solution of bis(4-methoxyphenyl)iodonium tetrafluoroborate (3.14 g, 6.12 mmol, Yokoyama *et al. J. Med. Chem.* 38:695 (1995)) and copper powder (0.52 g, 8.12 mmol) in  $CH_2Cl_2$  (12.0 mL) at 0 °C was added a solution of 2,6-dibromo-4-nitrophenol (1.20 g, 4.04 mmol) and  $Et_3N$  (0.62 mL, 4.48 mmol) in  $CH_2Cl_2$  (8.0 mL). The reaction was wrapped in aluminum foil (darkness), stirred at room temperature for 216 h and filtered through a Celite plug. The filtrate was concentrated and purified by column chromatography on silica gel, eluting with acetone-hexanes (3: 97) to afford 3,5-dibromo-4-(3'-isopropyl-4'-methoxyphenoxy)nitrobenzene as an orange solid (1.95 g, 100%): <sup>1</sup>H NMR (300 MHz,  $DMSO-d_6$ ):  $\delta$  8.60 (s, 2H), 6.82 (m, 2H), 6.44 (m, 1H), 3.73 (s, 3H), 3.12 (m, 1H), 1.13 (d,  $J = 6.0$  Hz, 6H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (3:47);  $R_f = 0.45$ .

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## Step b:

[1045] To a stirred solution of 3,5-dibromo-4-(3'-isopropyl-4'-methoxyphenoxy)-nitrobenzene (1.37 g, 2.98 mmol) in  $\text{CH}_2\text{Cl}_2$  (30.0 mL) at -78 °C was added  $\text{BBr}_3$  (8.93 mL, 8.93 mmol, 1 M solution in  $\text{CH}_2\text{Cl}_2$ ). The reaction mixture was stirred at room temperature for 2.5 h, quenched with ice/water, and stirred cold for several minutes. The reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  and  $\text{H}_2\text{O}$ , partitioned, and the aqueous solution was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were concentrated under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1: 10) to afford 3,5-dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)nitrobenzene as a solid (1.20 g, 90%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.19 (s, 1H), 8.64 (s, 2H), 6.73 (m, 2H), 6.37 (m, 1H), 3.12 (m, 1H), 1.16 (d,  $J = 6.0$  Hz, 6H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:5);  $R_f = 0.46$ .

## Step c:

[1046] To a stirred solution of 3,5-dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)nitrobenzene (0.43 g, 0.96 mmol) in  $\text{CH}_2\text{Cl}_2$  (9.0 mL) at 0 °C was added diisopropylethylamine (0.50 mL, 2.89 mmol) and the reaction mixture was stirred for several minutes. Chloromethylmethyl ether (0.15 mL, 1.92 mmol) was added and the solution was refluxed for 16 h, cooled to 0 °C, quenched with  $\text{H}_2\text{O}$  and partitioned between  $\text{CH}_2\text{Cl}_2$  and  $\text{H}_2\text{O}$ . The organic layer was concentrated under reduced pressure and coevaporated with methanol and toluene to afford 3,5-dibromo-2-(3'-isopropyl-4'-methoxymethoxyphenoxy)nitrobenzene as a glass (0.430 g, 91%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.65 (s, 2H), 7.00 (m, 1H), 6.86 (m, 1H), 6.48 (m, 1H), 5.19 (s, 2H), 3.41 (s, 3H), 3.14 (m, 1H), 1.17 (d,  $J = 6.0$  Hz, 6H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:5);  $R_f = 0.50$ .

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Step d:

[1047] To a stirred suspension of 3,5-dibromo-2-(3'-isopropyl-4'-methoxymethoxyphenoxy)nitrobenzene (0.72 g, 1.47 mmol) in MeOH/H<sub>2</sub>O (15.0 mL/3.0 mL) was added Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> (2.56 g, 14.68 mmol). The reaction mixture was stirred at room temperature for 20 min and the methanol was evaporated under reduced pressure. The reaction mixture was diluted with diethyl ether and H<sub>2</sub>O, partitioned, and the aqueous solution was treated with 1:1 saturated aqueous NaHCO<sub>3</sub> /brine. The treated aqueous layer was then extracted with ethyl acetate. The organic layers were then combined, washed with H<sub>2</sub>O (2X), concentrated, then coevaporated with MeOH (2X) to afford 3,5-dibromo-4-(3'-isopropyl-4'-methoxymethoxyphenoxy)aniline as a solid (0.60 g, 89%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 6.93 (m, 3H), 6.72 (m, 1H), 6.40 (m, 1H), 5.16 (s, 2H), 3.40 (s, 3H), 3.21 (m, 1H), 1.15 (d, J = 6.0 Hz, 6H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:5); R<sub>f</sub> = 0.27.

Step e:

[1048] To a stirred suspension of 3,5-dibromo-4-(3'-isopropyl-4'-methoxymethoxyphenoxy)aniline (0.50 g, 1.12 mmol) in THF (12.0 mL) was added *t*-BOC anhydride (0.61 g, 2.80 mmol), dimethylaminopyridine (0.025 g, 5% wt/wt), and *t*-BuOH (0.25 g, 3.36 mmol). The reaction mixture was stirred at reflux for 1 h and the solvent was evaporated under reduced pressure. The reaction mixture was diluted with ethyl acetate and H<sub>2</sub>O, partitioned, and the organic layer was concentrated. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1: 10) to afford *t*-butyl *N*-*t*-butoxycarbonyl-[3,5-dibromo-4-(3'-isopropyl-4'-methoxymethoxyphenoxy)phenyl]carbamate as a solid (0.62 g, 86%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.84 (s, 2H), 7.04 (m, 1H), 6.66 (m, 1H), 6.51 (m, 1H), 5.18 (s, 2H), 3.41 (s, 3H), 3.15 (m, 1H), 1.22 (s, 18H), 1.13 (d, J = 6.0 Hz, 6H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:5); R<sub>f</sub> = 0.68.

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## Step f:

[1049] To a stirred solution of *t*-butyl *N*-*t*-butoxycarbonyl-[3,5-dibromo-4-(3'-isopropyl-4'-methoxymethoxyphenoxy)phenyl]carbamate (0.62 g, 0.96 mmol) in methanol (20.0 mL) was added 2 M NaOH (2.88 mL, 5.77 mmol). The reaction mixture was stirred at rt for 4.5 h and the solvent was evaporated under reduced pressure. The reaction mixture was treated with saturated aqueous ammonium chloride, diluted with ethyl acetate and H<sub>2</sub>O, partitioned, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO<sub>4</sub>, and concentrated to afford *t*-butyl [3,5-dibromo-4-(3'-isopropyl-4'-methoxymethoxyphenoxy)phenyl]carbamate as an oil (0.62 g, 86%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.79 (s, 1H), 7.87 (s, 2H), 6.97 (m, 1H), 6.77 (m, 1H), 6.39 (m, 1H), 5.17 (s, 2H), 3.41 (s, 3H), 3.14 (m, 1H), 1.50 (s, 9H), 1.17 (d, J = 6.0 Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:5); R<sub>f</sub> = 0.68.

## Step g:

[1050] To a stirring mixture of *t*-butyl [3,5-dibromo-4-(3'-isopropyl-4'-methoxymethoxyphenoxy)phenyl]carbamate (0.11 g, 0.20 mmol) and acetonitrile (3.0 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (0.859 g, 2.64 mmol) followed by ethyl [(4-methylphenyl)sulfonyloxymethyl]methylphosphinate (compound 74, 0.059 g, 0.20 mmol). The reaction mixture was stirred at reflux for 16 h then partitioned with ethyl acetate and H<sub>2</sub>O. The organic layer was concentrated and the crude product was purified by preparatory thin-layer chromatography on silica gel, eluting with ethyl acetate-hexanes (4:1) to afford ethyl *N*-*t*-butoxycarbonyl-[(3,5-dibromo-4-(3'-isopropyl-4'-methoxymethoxyphenoxy)phenylamino)methyl]methylphosphinate as an oil (0.053 g, 39%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.88 (s, 2H), 6.99 (m, 1H), 6.72 (m, 1H), 6.47 (m, 1H), 5.18 (s, 2H), 4.13 (m, 2H), 3.93 (m, 1H), 3.75 (m, 1H), 3.41 (s, 3H), 3.14 (m, 1H), 1.43 (s, 9H), 1.12 (d, J = 6.0 Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (4:1); R<sub>f</sub> = 0.17.

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Step h:

[1051] To a mixture of ethyl *N*-*t*-butoxycarbonyl-[(3,5-dibromo-4-(3'-isopropyl-4'-methoxymethoxyphenoxy)phenylamino)methyl]methylphosphinate (0.27 g, 0.41 mmol) in methanol (6.0 mL) was added 3 N HCl (0.68 mL, 2.03 mmol). The reaction mixture was heated with microwave radiation at 100 °C in a sealed vial for 5 minutes. The solvent was removed and the residue was partitioned with ethyl acetate and brine, partitioned, and the aqueous solution was extracted with ethyl acetate. The combined organic layers were coevaporated with methanol and concentrated under reduced pressure. The crude residue was purified by preparatory thin-layer chromatography on silica gel, eluting with methanol-ethyl acetate (5:95) to afford ethyl [(3,5-dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)phenylamino)methyl]methylphosphinate (0.16 g, 77%) as an oil: <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.97 (s, 1H), 7.11 (s, 2H), 6.65 (m, 2H), 6.26 (m, 2H), 4.06 (m, 2H), 3.55 (m, 2H), 3.14 (m, 1H), 1.48 (d, J = 6.0 Hz, 6H), 1.22 (m, 3H), 1.12 (d, J = 6.0 Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = methanol-ethyl acetate (5:95); R<sub>f</sub> = 0.35.

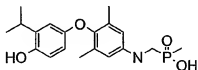
Step i:

[1052] To a solution of ethyl [(3,5-dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)phenylamino)methyl]methylphosphinate (0.08 g, 0.16 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) at -30 °C was added bromotrimethylsilane (0.21 mL, 1.55 mmol). The reaction mixture was stirred at -30 °C for 4 h, then rt for 12 h and the solvent was removed under reduced pressure. The residue was treated with acetonitrile- H<sub>2</sub>O (4:1, 5.0 mL) and stirred at 38 °C for 30 min. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with H<sub>2</sub>O. The organic solution was filtered and concentrated under reduced pressure to afford the title compound as an off-white powder (0.076 g, 100%); <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 6.92 (s, 2H), 6.51 (m, 2H), 6.20 (m, 1H), 3.38 (m, 2H), 3.12 (m, 1H), 1.43 (d, J = 15.0 Hz, 3H), 1.05 (d, J = 6.0 Hz, 6H); LC-MS *m/z* = 494 [C<sub>17</sub>H<sub>20</sub>Br<sub>2</sub>NO<sub>4</sub>P - H]<sup>+</sup>;

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HPLC conditions: Column = Shimadzu LC-A8, SPD-10A; YMC Pack RP-18 filter, 150×4.6; Mobile phase = Solvent A Acetonitrile/0.05% TFA; Solvent B = H<sub>2</sub>O/0.05% TFA. Flow rate = 2.0 mL/min; UV@ 254 nm. rt = 14.52 min

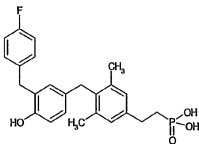
**Compound 84-2:** [(3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenylamino)methyl]methylphosphinic acid



[1053] The title compound was prepared from 2,6-dimethyl-4-nitrophenol according to the procedure described for the synthesis of example 84, steps a-i. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.17 (s, 2H), 6.58 (m, 2H), 6.28 (m, 1H), 3.78 (m, 2H), 3.20 (m, 1H), 2.12 (s, 6H), 1.52 (d, *J* = 15.0 Hz, 3H), 1.11 (d, *J* = 7.5 Hz, 6H); Anal. Calcd for (C<sub>19</sub>H<sub>26</sub>NO<sub>4</sub>P + 1 HBr + 0.7 H<sub>2</sub>O): C, 49.95; H, 6.26; N, 3.07. Found: C, 49.70; H, 6.04; N, 2.69. LC-MS *m/z* = 364 [C<sub>19</sub>H<sub>26</sub>NO<sub>4</sub>P-H]<sup>+</sup>; HPLC conditions: Column = Kromasil; C18-100×4.6 mm; Mobile phase = Solvent A: MeOH; Solvent B: H<sub>2</sub>O/0.05% TFA. Flow rate = 1.0 mL/min; UV@ 280 nm. Retention time in minutes. (rt = 11.48/25.00, 96% purity).

### Example 85

**Compound 85:** 2-[3,5-Dimethyl-4-(3'-(4-fluorobenzyl)-4'-hydroxybenzyl)phenyl]ethylphosphonic acid



[1054] The title compound was prepared from dimethyl 2-[3,5-Dimethyl-4-(3'-(4-fluorobenzyl)-4'-hydroxybenzyl)phenyl]ethylphosphonate (compound

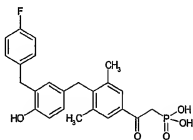


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78, step k) according to the procedure described for the synthesis of compound 7, step b (40 mg, 100%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.17 (s, 1 H), 7.11 (m, 4 H), 6.85 (s, 2 H), 6.53 – 6.73 (m, 3 H), 3.76 (s, 4 H), 2.64 (m, 2 H), 2.12 (s, 6 H), 1.78 (m, 2 H); LC-MS  $m/z$  = 429  $[\text{C}_{24}\text{H}_{26}\text{FO}_4\text{P} + \text{H}]^+$ ; Anal Calcd for  $(\text{C}_{24}\text{H}_{26}\text{FO}_4\text{P} + 2.3\text{H}_2\text{O})$ : C, 61.35; H, 6.56. Found: C, 61.04; H, 6.36.

### Example 86

**Compound 86:** dimethyl [2-(3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl)phenyl)-2-oxo-ethyl]phosphonic acid

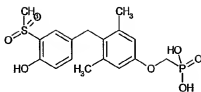


[1055] The title compound was prepared from (60 mg, 94%) from dimethyl [2-(3,5-dimethyl-4-(3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl)phenyl)-2-oxo-ethyl]phosphonate (compound 78, step h) according to the procedure described for the synthesis of compound 7, step b (60 mg, 94%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.23 (s, 1 H), 7.66 (s, 2 H), 7.15 (m, 2 H), 7.07 (m, 2 H), 6.76 (d,  $J$  = 2.1 Hz, 1 H), 6.66 (d,  $J$  = 8.1 Hz, 1 H), 6.55 (dd,  $J$  = 2.1, 8.1 Hz, 1 H), 3.90 (s, 2 H), 3.77 (s, 2 H), 3.47 (d,  $J$  = 22.5 Hz, 2 H), 2.23 (s, 6 H); LC-MS  $m/z$  = 443  $[\text{C}_{24}\text{H}_{24}\text{FO}_3\text{P} + \text{H}]^+$ ; Anal Calcd for  $(\text{C}_{24}\text{H}_{24}\text{FO}_3\text{P} + 0.1\text{HBr} + 0.2\text{EtOAc} + 0.8\text{H}_2\text{O})$ : C, 61.73; H, 5.70; Br, 1.66. Found: C, 61.59; H, 5.64; Br, 1.84.

### Example 87

**Compound 87:** [4-(4-Hydroxy-3-methanesulfonylbenzyl)-3,5-dimethylphenoxyethyl]-phosphonic acid

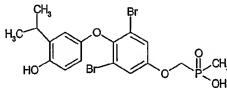
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[1056] The title compound was prepared from (compound 76, step a) according to the procedure described for the synthesis of compound 7, step b:  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  10.82 (s, 1 H), 7.33 (d,  $J = 2.0$  Hz, 1 H), 7.11 (dd,  $J = 2.0, 8.4$  Hz, 1 H), 6.95 (d,  $J = 8.4$  Hz, 1 H), 6.72 (s, 2 H), 4.03 (d,  $J = 10.2$  Hz, 2 H), 3.88 (s, 2 H), 3.20 (s, 3 H), 2.15 (s, 6 H); LC-MS  $m/z = 401$  [ $\text{C}_{17}\text{H}_{21}\text{O}_7\text{PS} + \text{H}$ ] $^+$ ; Anal Calcd for ( $\text{C}_{17}\text{H}_{21}\text{O}_7\text{PS} + 0.8\text{H}_2\text{O}$ ): C, 49.23; H, 5.49. Found: C, 49.11; H, 5.61.

### Example 88

**Compound 88:** [(3,5-dibromo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenoxy)methyl]methylphosphinic acid



Step a:

[1057] To a stirring mixture of DMF (20.0 mL) and NaH (0.074 g, 1.86 mmol) at 0 °C was added 3,5-dibromo-4-(3-isopropyl-4-hydroxyphenoxy)phenol (Intermediate for the synthesis of compound 8-1, 0.75 g, 1.86 mmol) dissolved in DMF (2.0 mL). The reaction mixture was allowed to stir at rt 1 hr and cooled to 0 °C. To the stirred mixture was ethyl [(4-methylphenyl)sulfonyloxymethyl]methylphosphinate (compound 74, 0.52 g, 1.77 mmol) and the reaction was stirred at rt for 16 h. The reaction was quenched with ice/ $\text{H}_2\text{O}$  and the solvent was evaporated. The pH was adjusted to 1 with 2 M HCl and the mixture was partitioned with ethyl acetate and  $\text{H}_2\text{O}$ . The aqueous solution was extracted with ethyl acetate and the combined

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organic layers were concentrated under reduced pressure was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (9:1) to afford crude product mixture (555 mg) and recovered starting material (270 mg). The crude product residue was treated with acetone to afford ethyl [(3,5-dibromo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenoxy)methyl]methylphosphinate as a white solid (0.23 g, 24%):  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  9.03 (s, 1 H), 7.50 (s, 2 H), 6.67 (m, 2 H), 6.27 (m, 1 H), 4.49 (m, 2 H), 4.02 (m, 2 H), 3.14 (m, 1 H), 1.58 (d,  $J$  = 16.0 Hz, 3 H); 1.23 (m, 3 H), 1.12 (d,  $J$  = 6.0 Hz, 6 H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate;  $R_f$  = 0.26

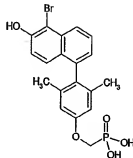
## Step b:

[1058] To a stirring suspension of ethyl [(3,5-dibromo-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenoxy)methyl]methylphosphinate (0.24, 0.45 mmol) in  $\text{CH}_2\text{Cl}_2$  (6.0 mL) at - 30 °C was added bromotrimethylsilane (0.59 mL, 4.50 mmol). The reaction mixture was stirred at rt for 16 h and the solvent was removed under reduced pressure. The residue was treated with acetonitrile-  $\text{H}_2\text{O}$  (5:1, 5.0 mL) and stirred at 38 °C for 20 min. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with  $\text{H}_2\text{O}$ . The organic solution was concentrated, coevaporated with MeOH, and filtered to afford the title compound as a white powder (0.215 g, 97%);  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  9.02 (s, 1 H), 7.47 (s, 2 H), 6.63 (m, 2 H), 6.26 (m, 1 H), 4.26 (d,  $J$  = 12.0 Hz, 2 H), 3.14 (m, 1 H), 1.45 (d,  $J$  = 14.0 Hz, 3 H), 1.12 (d,  $J$  = 6.0 Hz, 6 H); LC-MS  $m/z$  = 495  $[\text{C}_{17}\text{H}_{20}\text{Br}_2\text{O}_3\text{P} - \text{H}]^+$ ; Anal. Calcd for  $(\text{C}_{17}\text{H}_{20}\text{Br}_2\text{O}_3\text{P} + 0.2 \text{ H}_2\text{O} + 0.1 \text{ CH}_3\text{COCH}_3)$ : C, 41.27; H, 4.00 Found: C, 41.22; H, 4.06 HPLC conditions: Column = Shimadzu LC-A8, SPD-10A; YMC Pack RP-18 filter, 150 $\times$ 4.6; Mobile phase = Solvent A Acetonitrile/0.05% TFA; Solvent B =  $\text{H}_2\text{O}$ /0.05% TFA. Flow rate = 2.0 mL/min; UV@ 254 nm. Retention time. (rt = 8.93 min).

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## Example 89

**Compound 89:** [4-(5'-bromo-6'-hydroxynaphthyl)-3,5-dimethylphenoxy]-methylphosphonic acid



Step a:

[1059] To a stirred solution of 6-methoxy-1-naphthol (Kasturi, T.R. Arunachalam, T. *Can. Journal. Chem.* 3625 (1968), 3.0 g, 17.2 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (50 mL) at  $-40^\circ\text{C}$  was added  $\text{Et}_3\text{N}$  (4.66 mL, 34.4 mmol) and the reaction mixture was stirred at  $-40^\circ\text{C}$  for 15 min. Trifluoromethanesulfonyl anhydride (5.8 g, 20.6 mmol)  $\text{CH}_2\text{Cl}_2$  in (5 mL) was added and the reaction mixture was stirred for 2 h at  $-10^\circ\text{C}$  and for 30 min at room temperature. The reaction mixture was quenched with saturated  $\text{NaHCO}_3$  (50 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (2x100 mL). The combined organic layers were washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:9) to afford 6-methoxy-1-naphthyl trifluoromethanesulfonate as a colorless oil (5.10 g, 92%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.0 (d,  $J = 9.0$  Hz, 1H), 7.77 (d,  $J = 8.4$  Hz, 1H), 7.44 (t,  $J = 8.1$  Hz, 1H), 7.35-7.32 (m, 2H), 7.22 (s, 1H), 3.98 (s, 3H); TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (1:4);  $R_f = 0.6$ .

Step b:

[1060] A mixture of 6-methoxy-1-naphthyl trifluoromethanesulfonate (0.85 g, 2.6 mmol), bis-picolinato-diborane (1.07 g, 3.95 mmol) and anhydrous

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potassium acetate (0.77 g, 7.8 mmol) in DMSO (30 mL) was degassed by nitrogen sparge for 30 min and PdCl<sub>2</sub>dppf.dichloromethane (0.43 g, 0.52 mmol) was added. The reaction mixture was heated to 85 °C for 4 h. The reaction mixture was filtered through a Celite plug and washed with ethyl acetate (2x50 mL) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:4) to afford 1,1,2,2-tetramethyl-6-methoxynaphthyl-1-boronate as a pale yellow solid (0.64 g, 86%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.69 (d, *J* = 9.3 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.46 (dd, *J* = 1.5, 6.6 Hz, 1H), 7.22 (dd, *J* = 2.4, 9.0 Hz, 1H), 7.16 (d, *J* = 2.4 Hz, 1H), 3.96 (s, 3H), 1.45 (s, 12H); TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (1:4); R<sub>f</sub> = 0.65.

## Step c:

- [1061] To a stirred suspension of NaH (0.5 g, 22.0 mmol) in anhydrous DMF (20 mL) at 0 °C was added 3,5-dimethyl-4-bromophenol (2.2 g, 11.0 mmol) in DMF (5 mL) followed by diethyl tosyloxymethylphosphonate (3.9 g, 24.2 mmol) in DMF (5.0 mL) 30 min later. The reaction mixture was stirred for 14 h at room temperature and poured into water (30 mL). The aqueous solution was extracted with ethyl acetate (2x100 mL) and the combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (2:3) to afford diethyl (3,5-dimethyl-4-bromophenoxy)methylphosphonate as a syrup. (1.85 g, 48%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 6.88 (s, 2H), 4.15-4.25 (m, 6H), 2.41 (s, 2H), 1.40 (t, *J* = 6.0 Hz, 6H); LC-MS *m/z* = 351[C<sub>13</sub>H<sub>20</sub>BrO<sub>4</sub>P+H]<sup>+</sup>; TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (2:3); R<sub>f</sub> = 0.3.

## Step d:

- [1062] To a stirred solution of 1,1,2,2-tetramethyl-6-methoxynaphthyl-1-boronate (0.5 g, 1.76 mmol) and diethyl (3,5-dimethyl-4-

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bromophenoxy)methylphosphonate (0.675 g, 1.93 mmol) in anhydrous DME (40 mL) degassed by nitrogen for 10 min. Palladium tetrakis(triphenylphosphine) (0.4 g, 0.35 mmol) and an aqueous solution of sodium carbonate (0.55 g, 5.28 mmol) in water (10 mL) were added. The reaction mixture was heated 85 °C for 24 h. and the reaction mixture was poured into water (30 mL). The aqueous solution was extracted with ethyl acetate (2x100 mL) and the combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:2) to afford diethyl [3,5-dimethyl-4-(6'-methoxynaphthyl)phenoxy]methylphosphonate as a syrup. (0.45 g, 45%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.77 (d, *J* = 8.1 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 6.0 Hz, 1H), 7.24-7.23 (m, 2H), 7.13 (d, *J* = 1.5 Hz, 1H), 7.05 (dd, *J* = 2.7, 9.0 Hz, 1H), 6.81 (s, 2H), 4.34-4.27 (m, 6H), 3.96 (s, 3H), 1.91 (s, 6H), 1.42 (t, *J* = 5.1 Hz, 6H); LC-MS *m/z* = 429 [C<sub>24</sub>H<sub>25</sub>O<sub>3</sub>P+H]<sup>+</sup>; TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (2:3); R<sub>f</sub> = 0.3.

## Step e:

[1063] To a stirred solution of diethyl [3,5-dimethyl-4-(6'-methoxynaphthyl)phenoxy]methylphosphonate (130 mg, 0.30 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added bromine (50 mg, 0.32 mmol), the solution was stirred for 30 min. and the reaction mixture was washed with aqueous sodium bisulfate. The resulting solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x50 mL) and the combined organic layers were washed with saturated NaHCO<sub>3</sub> (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (2:3) to afford diethyl [4-(5'-bromo-6'-methoxynaphthyl)-3,5-dimethylphenoxy]methylphosphonate as a brownish solid (140 mg, 93%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.30 (d, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.34-7.32 (m, 2H), 7.20-7.15 (m, 2H), 6.82 (s, 2H), 4.39-4.29 (m, 6H), 4.04 (s, 3H), 1.90 (s, 6H), 1.44 (t, *J* = 6.9 Hz, 6H); LC-MS

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$m/z = 507$  [ $C_{24}H_{28}BrO_3P$ ] $^+$ ; TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (2:3);  $R_f = 0.28$ .

Step f:

[1064] To a stirred solution of diethyl [4-(5'-bromo-6'-methoxynaphthyl)-3,5-dimethylphenoxy]methylphosphonate (130 mg, 0.25 mmol) in  $CH_2Cl_2$  (5 mL) at 0 °C was added TMSBr (0.38 g, 0.35 mL, 2.5 mmol). The reaction mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature and stirred for 16 h. The solvent was removed under reduced pressure, the residue was dissolved in  $CH_3OH$  (3 mL) and the solvent was removed under reduced pressure. The residue was triturated with acetonitrile and dried under reduced pressure to afford [4-(5'-bromo-6'-methoxynaphthyl)-3,5-dimethylphenoxy]methylphosphonic acid as a white solid (0.12 g 100%, crude):  $^1H$  NMR (300 MHz,  $CD_3OD$ ):  $\delta$  8.12 (d,  $J = 8.8$  Hz, 1H), 7.55 (t,  $J = 7.0$  Hz, 1H), 7.13-6.92 (m, 3H), 6.80 (s, 2H), 4.20 (d,  $J = 10.4$  Hz, 2H), 3.96 (s, 3H), 1.91 (s, 6H); LC-MS  $m/z = 451$  [ $C_{20}H_{20}BrO_3P$ ] $^+$ ;

Step g:

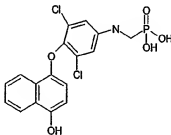
[1065] To a stirred solution of [4-(5'-bromo-6'-methoxynaphthyl)-3,5-dimethylphenoxy]methylphosphonic acid (0.12 g, 0.26 mmol) in  $CH_2Cl_2$  (5 mL) at -78 °C was added  $BBr_3$  (0.1 g, 0.39 mmol) in  $CH_2Cl_2$  (5 mL). The reaction mixture was stirred at rt for 3 h and poured into ice water (25 mL) and stirred for 1 h. The reaction mixture was extracted with ethyl acetate (2x50 mL). The combined organic layers were washed with water and brine, dried over  $Na_2SO_4$ , filtered and concentrated under reduced pressure. The crude product was recrystallized from  $CH_2Cl_2$ , filtered and dried under reduced pressure to afford the title compound as a yellow solid (70 mg, 92%, 94% pure):  $^1H$  NMR (200 MHz,  $CD_3OD$ ):  $\delta$  8.14 (d,  $J = 8.8$  Hz, 1H), 7.39 (t,  $J = 7.0$  Hz, 1H), 7.15-6.99 (m, 3H), 6.81 (s, 2H), 4.19 (d,  $J = 10.4$  Hz, 2H), 1.81 (s, 6H); LC-MS  $m/z = 437$  [ $C_{19}H_{18}BrO_3P+H$ ] $^+$ ; HPLC conditions: YMC pack ODS-AQ12S051546W column; mobile phase = TFA/ACN (0.05%) and TFA/ $H_2O$  (0.05%) flow rate = 1.0 mL/min; detection = UV@254 nm retention

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time in min: 7.14; Anal Calcd: (MF: C<sub>19</sub>H<sub>18</sub>BrO<sub>3</sub>P+0.8 CH<sub>2</sub>Cl<sub>2</sub>) Calcd: C:47.36, H:3.92, Found: C: 47.12, H:3.58.

### Example 90

**Compound 90:** [3,5-dichloro-4-(4'-*O*-hydroxynaphthoxy)phenylamino]-methylphosphonic acid



Step a:

[1066] To a stirred solution of 4-methoxy-1-naphthol (0.5 g, 2.86 mmol) and 3,5-dichloro-4-iodonitrobenzene (1.0 g, 3.16 mmol) in DMSO (30 mL) at room temperature was added K<sub>2</sub>CO<sub>3</sub> (0.6 g, 4.30 mmol). The reaction mixture was heated at 125 °C for 18 h, cooled to room temperature and poured into water. The aqueous layer was extracted with ethyl acetate (2x100 mL). The combined organic layers were washed with brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1: 9) to afford 3,5-dichloro-4-(4'-*O*-methoxynaphthoxy)-nitrobenzene as a yellow solid (0.8 g, 78%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.15 (s, 2H), 8.0-8.16 (m, 1H), 7.40-7.50 (m, 3H), 6.34 (d, *J* = 8.4 Hz, 1H), 6.06 (d, *J* = 8.4 Hz, 1H), 3.76 (s, 3H); TLC conditions: Uniplate silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (1:4); R<sub>f</sub> = 0.7.

Step b:

[1067] A suspension of 3,5-dichloro-4-(4'-*O*-methoxynaphthoxy)-nitrobenzene (0.47 g, 2.6 mmol) in acetic acid (20 mL) and water (2 mL) was heated at 50 °C until all material was dissolved then cooled to rt. Iron powder



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(108 mg, 1.94 mmol) was added at room temperature and the reaction mixture was stirred overnight, filtered through a Celite plug and washed with EtOAc (100 mL). The filtrate was extracted with ethyl acetate (2x100 mL). The combined organic layers were washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give 3,5-dichloro-4-(4'-*O*-methoxynaphthoxy)aminobenzene as a brownish solid (0.32 g, 75%):  $^1\text{H}$  NMR (200 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  8.15 (dd,  $J = 2.2, 5.8$  Hz, 1H), 8.0 (dd,  $J = 2.2, 5.8$  Hz, 1H), 7.37-7.31 (m, 2H), 6.58 (s, 2H), 6.45 (d,  $J = 8.4$  Hz, 1H), 6.07 (d,  $J = 8.4$  Hz, 1H), 3.73 (s, 3H); TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (2:3);  $R_f = 0.3$ .

Step c:

[1068] To a stirred solution of 3,5-dichloro-4-(4'-*O*-methoxynaphthoxy)aminobenzene (**14**, 0.3 g, 0.90 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at 0 °C were added  $\text{Et}_3\text{N}$  (0.27 g, 2.25 mmol),  $(\text{Boc})_2\text{O}$  (0.21 g, 1.0 mmol) and a catalytic amount of DMAP (25 mg). The reaction mixture was stirred at rt for 4 h and quenched with water (15 mL). The reaction mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (2x50 mL). The combined organic layers were washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (2:8) to afford *t*-butyl *N*-[3,5-dichloro-4-(4'-*O*-methoxynaphthoxy)benzene]carbamate as a yellow solid (0.22 g, 58%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.21 (dd,  $J = 2.2, 6.0$  Hz, 1H), 8.04 (d,  $J = 2.2, 6.0$  Hz, 1H), 7.43-7.36 (m, 2H), 7.07 (s, 2H), 6.33 (d,  $J = 8.4$  Hz, 1H), 6.07 (d,  $J = 8.4$  Hz, 1H), 3.74 (s, 3H), 1.32 (s, 9H).

Step d:

[1069] To a stirred solution of *t*-butyl *N*-[3,5-dichloro-4-(4'-*O*-methoxynaphthoxy)benzene]carbamate (0.22 g, 0.5 mmol) in anhydrous acetonitrile (15 mL) at room temperature were added  $\text{Cs}_2\text{CO}_3$  (0.33 g, 1.0 mmol) and diethyl tosyloxymethylphosphonate (0.16 g, 0.5 mmol). The reaction mixture was heated at 80 °C for 8 h and cooled to room temperature,

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then poured into water (20 mL). The aqueous solution was extracted with ethyl acetate (2x50 mL) and the combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:1) to afford diethyl *N*-*t*-butoxycarbonyl-[3,5-dichloro-4-(4'-*O*-methoxynaphthyl-1-oxyl)phenylamino]methylphosphonate as a viscous oil. (145 mg, 50%):  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.21 (dd,  $J = 1.8, 7.4$  Hz, 1H), 8.04 (dd,  $J = 2.0, 6.2$  Hz, 1H), 7.43-7.36 (m, 2H), 7.24 (s, 2H), 6.33 (d,  $J = 8.4$  Hz, 1H), 6.07 (d,  $J = 8.4$  Hz, 1H), 4.0-3.86 (m, 6H), 3.75 (s, 3H), 1.29 (s, 12H), 1.11 (t,  $J = 6.9$  Hz, 6H); LC-MS  $m/z = 584$  [ $\text{C}_{28}\text{H}_{34}\text{Cl}_2\text{NO}_6\text{P}+2$ ] $^+$ ; TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (1:1);  $R_f = 0.3$ .

Step e:

[1070] [3,5-dichloro-4-(4'-*O*-methoxynaphthyl-1-oxyl)phenylamino]methylphosphonic acid was prepared from diethyl *N*-*t*-butoxycarbonyl-[3,5-dichloro-4-(4'-*O*-methoxynaphthyl-1-oxyl)phenylamino]methylphosphonate according to the procedure described for the synthesis of compound 89, step f; brownish solid (92 mg, 100%):  $^1\text{H}$  NMR (200 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  8.13 (dd,  $J = 2.2, 6.6$  Hz, 1H), 7.99 (dd,  $J = 2.6, 6.0$  Hz, 1H), 7.40-7.31 (m, 2H), 6.67 (s, 2H), 6.44 (d,  $J = 8.4$  Hz, 1H), 6.07 (d,  $J = 8.4$  Hz, 1H), 3.74 (s, 3H), 3.27 (d,  $J = 12.0$  Hz, 2H); LC-MS  $m/z = 427$  [ $\text{C}_{18}\text{H}_{16}\text{Cl}_2\text{NO}_5\text{P}+\text{H}$ ] $^+$ ;

Step f:

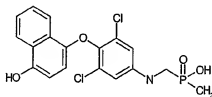
[1071] The title compound was prepared from [3,5-dichloro-4-(4'-*O*-methoxynaphthyl-1-oxyl)phenylamino]methylphosphonic acid according to the procedure described for the synthesis of compound 89, step g; brown solid (38 mg, 40%):  $^1\text{H}$  NMR (200 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  8.09 (dd,  $J = 2.2, 6.6$  Hz, 1H), 7.95 (dd,  $J = 2.6, 6.0$  Hz, 1H), 7.33-7.28 (m, 2H), 6.64 (s, 2H), 6.35 (d,  $J = 8.4$  Hz, 1H), 5.97 (d,  $J = 8.4$  Hz, 1H), 3.21 (d,  $J = 12.0$  Hz, 2H); LC-MS  $m/z = 414$  [ $\text{C}_{17}\text{H}_{14}\text{Cl}_2\text{NO}_5\text{P}+\text{H}$ ] $^+$ ; HPLC conditions: YMC pack ODS-AQ12S051546W column; mobile phase = TFA/ACN (0.05%) and TFA/ $\text{H}_2\text{O}$  (0.05%) flow rate = 1.0 mL/min; detection = UV@254 nm retention time in

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min: 9.58; Anal Calcd: (MF: C<sub>17</sub>H<sub>14</sub>Cl<sub>2</sub>NO<sub>3</sub>P+1.0 H<sub>2</sub>O) Calcd: C: 47.24, H: 3.73, N: 3.24 Found: C: 47.35, H: 3.51, N: 3.00.

### Example 91:

**Compound 91:** [(3,5-dichloro-4-(4'-*O*-hydroxynaphthoxy)phenylamino)methyl]methylphosphinic acid



#### Step a:

[1072] Ethyl *N*-*t*-butoxycarbonyl-[(3,5-dichloro-4-(4'-*O*-methoxynaphthoxy)-phenylamino)methyl]methylphosphinate was prepared from *t*-butyl *N*-[3,5-dichloro-4-(4'-*O*-methoxynaphthoxy)benzene]carbamate (compound 90, step c) and ethyl [(4-methylphenyl)sulfonyloxymethyl]methylphosphinate (compound 74) according to the procedure described for the synthesis of compound 90, step d; syrup (80 mg, 29%): <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 8.21 (dd, *J* = 1.8, 7.4 Hz, 1H), 8.04 (dd, *J* = 2.0, 6.2 Hz, 1H), 7.45-7.36 (m, 2H), 7.26 (s, 2H), 6.33 (d, *J* = 8.4 Hz, 1H), 6.06 (d, *J* = 8.4 Hz, 1H), 4.0-3.86 (m, 4H), 3.75 (s, 3H), 1.35 (d, *J* = 13.8 Hz, 3H), 1.29 (s, 12H), 1.07 (t, *J* = 6.9 Hz, 3H); LC-MS *m/z* = 555 [C<sub>26</sub>H<sub>32</sub>Cl<sub>2</sub>NO<sub>6</sub>P+H]<sup>+</sup>; TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (1:1); R<sub>f</sub> = 0.3.

#### Step b:

[1073] [(3,5-dichloro-4-(4'-*O*-methoxynaphthoxy)phenylamino)methyl]methylphosphinic acid was prepared from ethyl [(3,5-dichloro-4-(4'-*O*-methoxynaphthoxy)phenylamino)methyl]methylphosphinate according to the procedure described for the synthesis of compound 89, step f; brown solid (50 mg, 88%): <sup>1</sup>H NMR (200 MHz, CD<sub>3</sub>OD): δ 8.12 (dd, *J* = 2.2, 6.6 Hz, 1H), 7.98 (dd, *J* = 2.6, 6.0 Hz, 1H), 7.41-7.31 (m, 2H), 6.69 (s, 2H), 6.45 (d, *J* = 8.4

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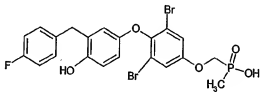
Hz, 1H), 6.07 (d,  $J = 8.4$  Hz, 1H), 3.74 (s, 3H), 3.29 (d,  $J = 12.0$  Hz, 2H), 1.38 (d,  $J = 14.0$  Hz, 3H); LC-MS  $m/z = 427$  [ $C_{18}H_{16}Cl_2NO_3P+H$ ] $^+$

Step c:

[1074] The title compound was prepared from [(3,5-dichloro-4-(4'-O-methoxynaphthoxy)phenylamino)methyl]methylphosphinic acid according to the procedure described for the synthesis of compound 89, step g; brownish solid (24 mg, 50%):  $^1H$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  9.58 (s, 1H), 8.01 (d,  $J = 7.8$  Hz, 1H), 7.89 (d,  $J = 7.8$  Hz, 1H), 7.48-7.34 (m, 2H), 6.73 (s, 2H), 6.43 (d,  $J = 8.0$  Hz, 1H), 5.99 (d,  $J = 8.0$  Hz, 1H), 3.13 (d,  $J = 10.4$  Hz, 2H) 1.14 (d,  $J = 13.8$  Hz, 3H); LC-MS  $m/z = 412$  [ $C_{18}H_{16}Cl_2NO_3P+H$ ] $^+$ .

### Example 92

**Compound 92:** [(3,5-Dibromo-4-(3'-(4-fluorobenzyl)-4'-hydroxyphenoxy)methyl)methylphosphinic acid



Step a

[1075] Ethyl [(3,5-Dibromo-4-(4'-hydroxy-3'-(4-fluorobenzyl)phenoxy)methyl)methyl phosphinate was prepared from 3,5-dibromo-4-[3'-(4-fluorobenzyl)-4'-hydroxyphenoxy] phenol (compound 82, step g) and ethyl [(4-methylphenyl)sulfonyloxymethyl]methylphosphinate (compound 74) according to the procedure described for the synthesis of compound 77, step a; (0.0148 gm, 14%);  $^1H$  NMR (200 MHz,  $CD_3OD$ ):  $\delta$  7.18 (s, 2H), 6.944 (m, 2H), 6.74 (t,  $J = 8.6$  Hz, 2H), 6.48 (d,  $J = 8.8$  Hz, 1H), 6.70 (m, 2H), 4.23 (dd,  $J = 5, 8.6$  Hz, 2H), 3.96 (m, 2H), 3.65 (s, 2H), 1.46 (d, 3 H,  $J = 14.6$  Hz), 1.16 (t,  $J = 7$  Hz, 3H); TLC conditions: Uniplat silica gel, 250 microns; ethyl acetate;  $R_f = 0.18$ ; LC-MS  $m/z$  589 [ $C_{23}H_{22}Br_2FO_3P+H$ ] $^+$ .

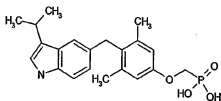
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Step b:

[1076] The title compound was prepared according to the procedure described for the synthesis of compound 7, step b; (0.010 gm, 81%);  $^1\text{H}$  NMR (200 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.36 (s, 2H), 7.14 (m, 2H), 6.94 (t,  $J = 8.8$  Hz, 2H), 6.65 (d,  $J = 8.4$  Hz, 1H), 6.70 (m, 2H), 4.28 (d,  $J = 8.6$  Hz, 2H), 3.96 (m, 2H), 3.85 (s, 2H), 1.65 (d, 3 H,  $J = 15.2$  Hz); TLC conditions: Uniplat silica gel, 250 microns; IPA/AcOH/ $\text{H}_2\text{O}$  [7:2:1];  $R_f = 0.73$ ; LC-MS  $m/z$  559  $[\text{C}_{21}\text{H}_{18}\text{Br}_2\text{FO}_5\text{P}-\text{H}]^-$ .

## Example 93

**Compound 93:** [3,5-Dimethyl-4-(3'-Isopropyl-1'-H-indol-5'-ylmethyl)-phenoxy]methylphosphonic acid



Step a:

[1077] To the suspension of 4-bromophenylhydrazine hydrochloride (6.0 g, 26.85 mmol) in water was added 3.5 M NaOH (11.5 ml, 40.82 mmol), followed by isovaleraldehyde (2.77g, 32.21 mmol). The reaction was stirred for 10 min, then the reaction was acidified with AcOH (25 ml). The reaction was stirred further for 30 min, and toluene was then added to extract the product twice. The combined toluene layer was washed with Sat.  $\text{NaHCO}_3$ , dried over  $\text{MgSO}_4$ , filtrated and concentrated to afford *N*-(4-bromo-phenyl)-*N'*-(3-methyl-butyl)-hydrazide (7.6 g, 100%):  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.63 (s, 1H), 7.07 (d,  $J = 8.6$  Hz, 1H), 6.97 (m, 1H), 6.62 (d,  $J = 8.6$  Hz, 2H), 1.88 (m, 2H), 1.60 (m, 1H), 0.71 (d,  $J = 6.6$  Hz, 6H).

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## Step b:

- [1078] To the solution of *N*-(4-bromo-phenyl)-*N'*-(3-methyl-butyl)-hydrazide (7.6 g, 31.54 mmol) in xylene (150 ml) was added  $\text{ZnCl}_2$  (5.16 g, 37.84 mmol). The reaction was refluxed for 1.5 hrs, then concentrated, and the residue was partitioned between toluene and sat.  $\text{NaHCO}_3$ . The organic layer was collected and the water layer was further extracted with toluene once. The combined organic layers was dried over  $\text{MgSO}_4$ , filtrated and concentrated. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:9) to afford 5-bromo-3-isopropyl-1H-indole (4.55 g, 60.9%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.72 (s, 1H), 8.57 (s, 1H), 8.05 (m, 2H), 7.77 (s, 1H), 3.95 (m, 1H), 2.15 (d,  $J$  = 6.6 Hz, 6H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:9);  $R_f$  = 0.51.

## Step c:

- [1079] To a suspension of NaH (509 mg, 20.16 mmol) in THF (50 ml) was added 5-bromo-3-isopropyl-1H-indole (4.55 g, 19.20 mmol). The reaction mixture was stirred at r.t. for 30 min, and TIPSCl was then added at r.t. The reaction was stirred further for 1 hr, diluted with EtOAc, and water was added to quench the reaction. The organic layer was collected and the water layer was further extracted with EtOAc once. The combined organic layer was dried over  $\text{MgSO}_4$ , filtrated and concentrated. The residue was purified by column chromatography on silica gel, eluting with hexane to afford 5-bromo-3-isopropyl-1-triisopropylsilyl-1H-indole (5.1 g, 67.6%):  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.53 (d,  $J$  = 1.8 Hz, 1H), 7.13 (d,  $J$  = 8.8 Hz, 1H), 6.99 (m, 1H), 6.76(s, 1H), 2.92 (m, 1H), 1.44 (m, 3H), 1.14 (d,  $J$  = 6.6 Hz, 6H), 0.93 (d,  $J$  = 7.4 Hz, 18H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = Hexane (1:9);  $R_f$  = 0.65.

## Step d:

- [1080] (2,6-Dimethyl-4-triisopropylsilyloxyphenyl)-(3-isopropyl-1-triisopropylsilyl-1H-indol-5-yl)-methanol was prepared from 5-bromo-3-

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isopropyl-1-triisopropylsilyl-1H-indole and 2,6-Dimethyl-4-triisopropylsilyloxybenzaldehyde according to the procedure described for the synthesis of compound 27, step c; brown oil (2.44g, 77.2%):  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.47 (s, 1H), 7.36 (d,  $J = 8.8$  Hz, 1H), 6.98 (d,  $J = 8.8$  Hz, 1H), 6.93 (s, 1H), 6.58 (s, 2H), 6.40 (d,  $J = 3.6$  Hz, 1H), 3.10 (m, 1H), 2.24 (s, 6H), 1.69 (m, 6H), 1.28 (d,  $J = 6.6$  Hz, 6H), 1.12 (d,  $J = 6.2$  Hz, 36H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:19);  $R_f = 0.62$ .

Step c:

[1081] To a solution of (2,6-dimethyl-4-triisopropylsilyloxyphenyl)-(3-isopropyl-1-triisopropylsilyl-1H-indol-5-yl)-methanol (1.86 g, 3.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 ml) was added triethylsilane (1.74 g, 15.0 mmol), followed by AcOH (1.11 ml), then TFA (1.11 ml, 15.0 mmol). The reaction was stirred at r.t. for 1 hr, the reaction mixture was diluted with EtOAc and water and the layers were separated. The EtOAc layer was collected and the water layer was further extracted with EtOAc once. The combined organic layers was washed with Sat.  $\text{NaHCO}_3$ , water and brine, dried over  $\text{MgSO}_4$ , filtrated and concentrated. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:49) to afford 5-(2,6-dimethyl-4-triisopropylsilyloxybenzyl)-3-isopropyl-1H-indole (1.0 g, 74.6%):  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.59 (s, 1H), 7.02 (d,  $J = 8.2$  Hz, 1H), 6.97 (s, 1H), 6.70 (s, 1H), 6.63 (d,  $J = 8.2$  Hz, 1H), 3.89 (s, 2H), 2.88 (m, 1H), 2.01 (s, 6H), 1.2 (m, 3H), 1.05 (d,  $J = 6.6$  Hz, 6H), 0.99 (d,  $J = 6.2$  Hz, 18H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:49);  $R_f = 0.70$ .

Step f:

[1082] 3,5-Dimethyl-4-(3-isopropyl-1H-indol-5-ylmethyl)phenol was prepared according to the procedure described for the synthesis of compound 35, step e; yellow oil (420mg, 64%):  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.61 (s, 1H), 7.06 (s, 1H), 7.02 (d,  $J = 8.0$  Hz, 1H), 6.72 (s, 1H), 6.63 (d,  $J = 8.2$  Hz,

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2H), 6.38 (s, 2H), 3.89 (s, 2H), 2.93 (s, 1H), 2.04 (s, 6H), 1.05 (d,  $J = 7.2$  Hz, 6H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:3);  $R_f = 0.65$ .

Step g:

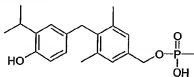
[1083] Diethyl [3,5-dimethyl-4-(3'-isopropyl-1'-H-indol-5'-ylmethyl)-phenoxy]methylphosphonate was prepared by the procedure used for the synthesis of compound 35, step f as a colorless oil (130 mg, 43%):  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.82 (s, 1H), 7.23 (s, 1H), 7.20 (d,  $J = 8.8$  Hz, 1H), 6.90 (s, 1H), 6.79 (d,  $J = 8.8$  Hz, 1H), 6.68 (s, 2H), 4.11 (m, 6H), 4.09 (s, 2H), 3.07 (m, 1H), 2.24 (s, 6H), 1.28 (m, 12H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:1);  $R_f = 0.65$ .

Step h:

[1084] The title compound was prepared according to the procedure described for the synthesis of compound 35, step h; yellow foam (50 mg, 63.6%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  10.60 (s, 1H), 7.18 (d,  $J = 8.0$  Hz, 1H), 7.13 (s, 1H), 6.98 (s, 1H), 6.71 (s, 2H), 6.63 (d,  $J = 8.0$  Hz, 1H), 4.02 (m, 4H), 3.02 (m, 1H), 2.20 (s, 6H), 1.22 (d,  $J = 7.0$  Hz, 6H). LC-MS  $m/z = 388$  [ $\text{C}_{21}\text{H}_{26}\text{NO}_4\text{P} + \text{H}^+$ ]; Anal. Calcd for ( $\text{C}_{21}\text{H}_{26}\text{NO}_4\text{P} + 0.5 \text{ HBr}$ ): C, 58.95; H, 6.24; N, 3.27. Found: C, 58.99; H, 6.42; N, 3.20.

### Example 94:

**Compound 94:** Methylphosphonic acid mono-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)benzyl] ester



Step a:

[1085] To a solution of 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)phenol (example 38, step c, 1.11 g, 3.52 mmol) and DMAP (1.72 g, 14.1 mmol) in  $\text{CH}_2\text{Cl}_2$  (27 mL) at  $0^\circ\text{C}$  was slowly added



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trifluoromethanesulfonyl anhydride (0.89 mL, 5.27 mmol). The reaction mixture was stirred at 0 °C for 2 h and quenched by water (10 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)-phenyl trifluoromethanesulfonate as an oil (1.39 g, 89%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.14 – 7.28 (m, 7H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 2.4 Hz, 1H), 6.70 (m, 1H), 5.15 (s, 2H), 3.94 (s, 2H), 3.88 (s, 2H), 3.27 (s, 3H), 2.24 (s, 6H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (15:85); R<sub>f</sub> = 0.55.

Step b:

- [1086] To a solution of 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)phenyl trifluoromethanesulfonate (1.36 g, 3.05 mmol) in DMF (15.3 mL) in a bomb apparatus was added MeOH (2.5 mL, 61.6 mmol), Pd(OAc)<sub>2</sub> (68 mg, 0.3 mmol), bis-(diphenylphosphino)propane (138 mg, 0.3 mmol) and Et<sub>3</sub>N (0.85 mL, 6.1 mmol). 60 psi of CO was then infused and the reaction mixture was stirred at 90 °C for 16 h. The cooled bomb was vented and the reaction mixture was poured into cold 1N HCl, extracted with EtOAc twice, the combined EtOAc were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtrated and concentrated. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:9) to afford methyl 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)benzoate as a yellow oil (1.00 g, 92.3%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.66 (s, 2H), 7.16 (m, 5H), 6.90 (m, 2H), 6.71 (m, 1H), 5.15 (s, 2H), 3.98 (s, 2H), 3.87 (s, 2H), 3.85 (s, 3H), 3.26 (s, 3H), 2.25 (s, 6H). TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (15:85); R<sub>f</sub> = 0.50.

Step c:

- [1087] To a mixture of methyl 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl)benzoate (1.00 g, 2.81 mmol) in THF (11.3 mL) at 0 °C was added a solution of DIBAL-H (8.44 mL, 8.44 mmol, 1.0 M solution in hexanes). The reaction mixture was stirred at room temperature for 16 h,

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quenched with cold 1 N HCl and diluted with ethyl acetate. The organic layer was washed with 1 N HCl and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxy-benzyl)benzyl alcohol as an off-white solid (0.75 g, 81.3%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.54 (s, 2H), 6.81 (m, 2H), 6.40 (m, 1H), 5.51 (m, 1H), 4.54 (d, *J* = 6.0 Hz, 2H), 3.75 (s, 3H), 3.21 (m, 1H), 1.13 (d, *J* = 6.0 Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (15:85); R<sub>f</sub> = 0.27.

Step d:

- [1088] To a mixture of 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxy-benzyl)benzyl alcohol (0.26 g, 0.79 mmol) in dichloromethane (1.5 mL) was added TEA (0.11 mL, 0.79 mmol) and a solution of methylphosphonic dichloride (0.11 g, 0.79 mmol) in dichloromethane (0.5 mL). The reaction mixture was stirred at room temperature for 2.75 h, filtered to remove salts, and the filtrate was then concentrated to remove dichloromethane. The reaction mixture was taken up in ethyl acetate, and extracted into 1N NaOH (2 x 10 mL). The basic layer was then acidified to pH = 2 with 1N HCl and extracted into ethyl acetate (2 x 10 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was then purified by preparative TLC 500 μm silica gel plate eluted with methanol / ethyl acetate [3 : 7] to give methylphosphonic acid mono-[3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxy-benzyl)benzyl] ester (55 mg, 17.1%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.07 (s, 2H), 6.94 (s, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.62 (d, *J* = 6.0 Hz, 1H), 5.14 (s, 2H), 5.00 (d, *J* = 7.5 Hz, 2H), 3.96 (s, 2H), 3.46 (s, 3H), 3.30-3.26 (m, *J* = 13.8 Hz, 1H), 2.24 (s, 6H), 1.56 (d, *J* = 18.3 Hz, 3H), 1.19 (d, *J* = 7.2 Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate; R<sub>f</sub> = 0.05.

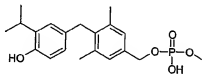
Step e:

- [1089] To a mixture of methylphosphonic acid mono-[3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxy-benzyl)benzyl] ester (40 mg, 0.10 mmol) in

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methanol (0.98 mL) was added 1N HCl (0.49 mL, 0.49 mmol). The reaction mixture was stirred at room temperature for 7 days and concentrated to remove methanol. The reaction mixture was taken up in ethyl acetate (5 mL) and 1N HCl (5 mL). The organic layer was rinsed with H<sub>2</sub>O, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was then purified by preparative TLC 250  $\mu$ m silica gel plate eluted with methanol-ethyl acetate [5 : 95] to give the title compound (7.0 mg, 19.6 %): <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  9.02 (s, 1H), 7.04 (s, 2H), 6.85 (s, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 6.46 (d, *J* = 7.0 Hz, 1H), 4.85 (d, *J* = 7.8 Hz, 2H), 3.87 (s, 2H), 3.16 (m, *J* = 14.4 Hz, 1H), 2.20 (s, 6H), 1.38 (d, *J* = 17.2 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = methanol-ethyl acetate [3 : 7]; R<sub>f</sub> = 0.70.

**Compound 94-1:** Phosphoric acid [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl) benzyl] ester methyl ester



Step a:

[1090] To a mixture of 3,5-dimethyl-4-(3'-*iso*-propyl-4'-methoxymethoxybenzyl) benzyl alcohol (0.10 g, 0.30 mmol) in methanol (1.5 mL) was added 1N HCl (1.5 mL, 1.5 mmol). The reaction mixture was stirred at 45°C for 16 h, then cooled to room temperature and concentrated to remove methanol. The reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. 3,5-dimethyl-4-(3'-*iso*-propyl-4'-hydroxybenzyl)benzyl alcohol (73 mg, 84.5%) was used without further purification: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.06 (s, 2H), 6.95 (s, 1H), 6.57 (m, *J* = 5.1 Hz, 2H), 4.64 (s, 2H), 3.96 (s, 2H), 3.17 (m, *J* = 14.1 Hz, 1H), 2.25 (s, 6H), 1.22 (d, *J* = 2.7 Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes [1 : 1]; R<sub>f</sub> = 0.54.

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## Step b:

- [1091] To a mixture of 3,5-dimethyl-4-(3'-*iso*-propyl-4'-hydroxybenzyl)-benzyl alcohol (73 mg, 0.26 mmol) in tetrahydrofuran (2.0 mL) was added *t*-BuMgCl (0.26 mL, 1.0 M in THF, 0.26 mmol) and dimethyl chlorophosphate (0.03 mL, 0.26 mmol). The reaction mixture was stirred at 45°C for 16 h, then cooled to room temperature and concentrated to remove dichloromethane. The reaction mixture was taken up in ethyl acetate, and extracted into 1N NaOH (2 x 10 mL). The basic layer was then acidified to pH = 2 with 1N HCl and extracted into ethyl acetate (2 x 10 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was then purified by preparative TLC 500 µm silica gel plate eluted with ethyl acetate-hexanes [7 : 3] to give phosphoric acid [3,5-dimethyl-4-(3'-*iso*-propyl-4'-hydroxybenzyl)benzyl] ester dimethyl ester (31 mg, 30.7%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.11 (d, *J* = 9.3 Hz, 2H), 7.05 (s, 2H), 7.00 (s, 1H), 6.67 (d, *J* = 10.5 Hz, 1H), 4.62 (s, 2H), 3.98 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.30 (m, *J* = 13.8 Hz, 1H), 2.22 (s, 6H), 1.20 (d, *J* = 6.9 Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes [1 : 1]; R<sub>f</sub> = 0.24.

## Step c:

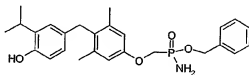
- [1092] To a solution of phosphoric acid [3,5-dimethyl-4-(3'-*iso*-propyl-4'-hydroxybenzyl)benzyl] ester dimethyl ester (31 mg, 0.08 mmol) in THF (0.4 mL) was added 1N NaOH (0.4 mL, 0.40 mmol). The reaction mixture was stirred at 60°C for 16 h, then cooled to room temperature and concentrated to remove solvent. The reaction mixture was taken up in ethyl acetate and extracted into 1N NaOH (2 x 10 mL). The basic layer was then acidified to pH = 2 with 1N HCl and extracted into ethyl acetate (2 x 10 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give the title compound (3.1 mg, 10.4%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.07 (m, 3H), 6.99 (s, 1H), 6.64 (d, *J* = 8.4 Hz, 2H), 4.63 (s, 2H), 3.99 (s, 2H), 3.79 (d, *J* = 11.4 Hz, 3H), 3.29 (m, 1H), 2.22 (s, 6H), 1.17 (d, *J* = 6.6 Hz, 6H);

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LC-MS  $m/z = 377.4$  [ $C_{20}H_{27}O_5P-H$ ]; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = methanol-ethyl acetate [3 : 7];  $R_f = 0.45$ .

### Example 95:

**Compound 95:** [4-(4-Hydroxy-3-isopropyl-benzyl)-3,5-dimethyl-phenoxy]methylphosphonic acid monobenzyl ester



Step a:

[1093] To a solution of [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-phenoxy]methylphosphonic acid (compound 7, 0.49 g, 1.36 mmol) in acetonitrile (13.6 mL), was added diisopropylethylamine (0.90 mL, 5.43 mmol) and benzyl bromide (0.65 mL, 5.43 mmol). The reaction mixture was stirred at 80°C for 16 h, then cooled to room temperature and concentrated to remove dichloromethane. The reaction mixture was taken up in ethyl acetate, rinsed with water, a saturated solution of sodium bicarbonate, and brine. The organic layer was dried over  $Na_2SO_4$ , filtered and concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel, eluted with ethyl acetate-hexanes [1 : 9] to give dibenzyl [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)phenoxy]methylphosphonate (0.50 g, 0.92 mmol):  $^1H$  NMR (200 MHz,  $DMSO-d_6$ ):  $\delta$  9.00 (s, 1H), 7.37 (m,  $J = 6.6$  Hz, 5H), 6.83 (s, 1H), 6.70 (s, 2H), 6.61 (d,  $J = 8.6$  Hz, 2H), 6.44 (d,  $J = 8.2$  Hz, 1H), 5.14 (d,  $J = 8.2$  Hz, 2H), 4.50 (d,  $J = 9.8$  Hz, 2H), 3.79 (s, 2H), 3.14 (m,  $J = 13.2$  Hz, 1H), 2.15 (s, 6H), 1.10 (d,  $J = 7.0$  Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes [1 : 1];  $R_f = 0.77$ .

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## Step b:

[1094] To a solution of dibenzyl [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)phenoxy]methylphosphonate (0.50 g, 0.92 mmol) in tetrahydrofuran (4.6 mL), was added 1N NaOH (4.6 mL, 4.6 mmol). The reaction mixture was allowed to stir at room temperature for 16 h. The reaction mixture was diluted in ethyl acetate and 1N NaOH. The organic layer was extracted with water, and then the pH was adjusted to pH = 12 with 1N NaOH. The aqueous layer was then extracted with ethyl acetate. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)phenoxy]methylphosphonic acid monobenzyl ester (0.45 g, 100%) as a yellow foam: <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 9.12 (s, 1H), 7.35 (m, *J* = 31.4 Hz, 5H), 6.84 (s, 1H), 6.64 (d, *J* = 10.2 Hz, 1H), 6.59 (s, 2H), 6.44 (d, *J* = 8.0 Hz, 1H), 4.83 (d, *J* = 7.0 Hz, 2H), 3.77 (m, *J* = 9.2 Hz, 4H), 3.15 (m, *J* = 14.0 Hz, 1H), 2.13 (s, 6H), 1.11 (d, *J* = 7.0 Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes [1 : 1]; R<sub>f</sub> = 0.04.

## Step c:

[1095] To a mixture of [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)phenoxy]methylphosphonic acid monobenzyl ester (108 mg, 0.238 mmol) and DMF (0.1 mL, 1.29 mmol) in dichloromethane (1.0 mL) at 0°C, was added oxalyl chloride (0.04 mL, 0.476 mmol). After 3 h, the reaction mixture was concentrated under reduced pressure, redissolved in dichloromethane (1.5 mL), and cooled to -78°C. To the reaction mixture triethylamine (0.07 mL, 0.476 mmol) was added, followed by liquid ammonia at -78°C (0.25 mL). The reaction mixture was stirred in a sealed vial warming to room temperature over 16 h. The vial was cooled to 0°C, vented and concentrated under reduced pressure. The reaction mixture was taken up in ethyl acetate and 1N NaOH. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was then purified by preparative TLC 1000 μm silica gel plate eluted with ethyl acetate to give [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)phenoxy]-methylphosphamic benzyl ester (18 mg, 16.7%):

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<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.40 (m, 5H), 6.93 (s, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.61 (s, 2H), 6.51 (d, *J* = 8.4 Hz, 1H), 5.17 (d, *J* = 8.1 Hz, 2H), 4.28 (dd, *J* = 10.5, 5.4 Hz, 2H), 3.89 (s, 2H), 3.22 (m, 1H), 2.19 (s, 6H), 1.22 (d, *J* = 6.6 Hz, 6H); LC-MS *m/z* = 454.4 [C<sub>26</sub>H<sub>32</sub>NO<sub>4</sub>P + H]<sup>+</sup>; TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate; R<sub>f</sub> = 0.56.

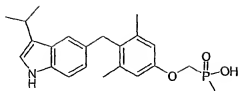
**Compound 95-1:** N-methyl-[4-(4-Hydroxy-3-isopropyl-benzyl)-3,5-dimethyl-phenoxy-methyl]-amino-phosphinic acid monobenzyl ester

[1096] To a mixture of [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-phenoxy]methylphosphonic acid monobenzyl ester (108 mg, 0.238 mmol) and DMF (0.1 mL, 1.29 mmol) in dichloromethane (1.0 mL) at 0°C, was added oxalyl chloride (0.04 mL, 0.476 mmol). After 3 h, the reaction mixture was concentrated under reduced pressure, redissolved in dichloromethane (1.5 mL), and cooled to -78°C. To the reaction mixture triethylamine (0.07 mL, 0.476 mmol) was added, followed by methylamine (0.24 mL, 2.0 M solution in THF, 0.476 mmol) at -78°C (0.25 mL). The reaction mixture was stirred, warming to room temperature over 16 h, then concentrated under reduced pressure. The reaction mixture was taken up in ethyl acetate and 1N NaOH. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was then purified by preparative TLC 1000 μm silica gel plate eluted with ethyl acetate to give N-methyl-[4-(4-Hydroxy-3-isopropyl-benzyl)-3,5-dimethyl-phenoxy-methyl]-amino-phosphinic acid monobenzyl ester (23 mg, 20.7%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.39 (m, 5H), 6.92 (s, 1H), 6.63 (s, 2H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.51 (d, *J* = 2.1 Hz, 1H), 5.14 (m, 2H), 5.05 (s, 1H), 4.30 (dd, *J* = 10.2, 3.6 Hz, 2H), 3.89 (s, 3H), 3.19 (m, 1H), 2.71 (d, *J* = 10.8 Hz, 3H), 2.19 (s, 6H), 1.22 (d, *J* = 6.9 Hz, 6H); LC-MS *m/z* = 468.4 [C<sub>27</sub>H<sub>34</sub>NO<sub>4</sub>P + H]<sup>+</sup>; TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate; R<sub>f</sub> = 0.44.

### Example 96

**Compound 96:** [(3,5-Dimethyl-4-(3'-Isopropyl-1'-H-indol-5'-ylmethyl)-phenoxy)methyl]methylphosphinic acid

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Step a:

[1097] To the solution of 3,5-dimethyl-4-(3-isopropyl-1H-indol-5-ylmethyl)phenol (compound 93, step f, 200 mg, 0.683mmol) in acetonitrile (10 ml) was added  $\text{Cs}_2\text{CO}_3$  (450 mg, 1.365 mmol), followed by ethyl [(4-methylphenyl)sulfonyloxymethyl]methylphosphinate (compound 74, 200 mg, 0.683 mmol) at r.t, the reaction mixture was then heated to reflux overnight. The second day, concentrated down, the residue was partitioned between EtOAc and water, collected the org. layer, water layer was further extracted with EtOAc once, the combined org. layer was dried over  $\text{MgSO}_4$ , filtrated and concentrated. The residue was purified by column chromatography on silica gel, eluting with ethyl MeOH- EtOAc (1:49) to afford ethyl [(3,5-dimethyl-4-(3'-Isopropyl-1'H-indol-5'-ylmethyl)phenoxy)methyl]-methylphosphinate (131 mg, 46.4%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.85 (s, 1H), 7.26 (s, 1H), 7.24 (d,  $J = 8.4$  Hz, 1H), 6.95 (s, 1H), 6.84 (d,  $J = 8.4$  Hz, 1H), 6.72 (s, 2H), 4.20 (m, 4H), 4.14 (s, 2H), 3.15 (m, 1H), 2.30 (s, 1H), 1.67 (d,  $J = 14.7$  Hz, 3H), 1.40 (m, 3H), 1.34 (d,  $J = 6.6$  Hz, 6H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate;  $R_f = 0.33$ .

Step b:

[1098] The title compound was prepared from ethyl [(3,5-dimethyl-4-(3'-Isopropyl-1'H-indol-5'-ylmethyl)phenoxy)methyl]methylphosphinate according to the procedure described for the synthesis of compound 93, step h; (100 mg, 81.3%):  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  10.58 (s, 1H), 7.17 (d,  $J = 8.4$  Hz, 1H), 7.13 (s, 1H), 6.98 (d,  $J = 1.8$  Hz, 1H), 6.72 (s, 2H), 6.67 (dd,  $J = 8.4, 1.8$  Hz, 1H), 4.08 (d,  $J = 8.4$  Hz, 2H), 3.99 (s, 2H), 2.98 (m, 1H), 2.19 (s, 6H), 1.40 (d,  $J = 14.4$  Hz, 3H), 1.22 (d,  $J = 6.9$  Hz, 6H). LC-MS  $m/z = 386$

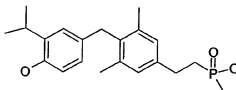


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$[\text{C}_{22}\text{H}_{28}\text{NO}_3\text{P} + \text{H}]^+$ ; Anal. Calcd for  $(\text{C}_{21}\text{H}_{26}\text{NO}_4\text{P} + 0.2 \text{ HBr})$ : C, 65.79; H, 7.08; N, 3.49. Found: C, 65.97; H, 7.28; N, 3.30.

## Example 97

**Compound 97:** {2-[3,5-Dimethyl-4-(4'-hydroxy-3'-isopropyl-benzyl)-phenyl]-ethyl}-methylphosphinic acid



## Step a:

[1099] Methyl 3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)-benzoate was prepared from 3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)-phenyl trifluoromethanesulfonate (intermediate for the synthesis of compound 24-1) according to the procedure described for the synthesis of compound 47, step a.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.68 (s, 2H), 6.97 (m, 1H), 6.91 (m, 2H), 6.20 (m, 1H), 5.16 (s, 2H), 4.01 (s, 3H), 3.85 (s, 3H), 3.21 (m, 1H), 2.28 (s, 6H), 1.14 (d,  $J = 6.0$  Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:4);  $R_f = 0.42$ .

## Step b:

[1100] DIBAL (11.4 mL) was added dropwise via addition funnel to a solution of methyl 3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)-benzoate (1.35 g) in THF (15 mL) at 0 °C. This reaction was stirred for 2h at 0 °C, at which point the cooling bath was removed and the reaction was allowed to warm to room temperature. The reaction was quenched with 0.5 M HCl, diluted with water and 100 mL 50/50 Hexanes/Ethyl Acetate. The layers were separated and dried ( $\text{MgSO}_4$ ). The solvents were removed by rotary evaporation, yielding 3,5-dimethyl-4-(3'-isopropyl-4'-

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methoxymethoxybenzyl)-benzyl alcohol (1.22 g, 97%) as a colorless oil.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  6.99 (s, 3H), 6.89 (d,  $J = 8.4$  Hz, 2H), 6.59 (m, 1H), 5.15 (s, 2H), 5.05 (t, 1H), 4.42 (d,  $J = 5.7$  Hz, 2H), 3.92 (s, 2H), 3.37 (s, 3H), 3.2 (m, 1H), 2.20 (s, 6H), 1.12 (d,  $J = 6.0$  Hz, 6H).

Step c:

[1101] 3,5-Dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)-benzyl alcohol (600 mg) in dichloromethane at 0 °C was treated with Dess-Martin Periodinane dropwise under a nitrogen atmosphere. The reaction mixture was warmed to room temperature over 3 hours, and stirred at room temperature for an additional 13 hours. A saturated solution of sodium bicarbonate solution was added, and the reaction was diluted with dichloromethane. The layers were separated and the organic layer was washed with brine and dried ( $\text{Na}_2\text{SO}_4$ ). The crude product was purified by column chromatography on silica gel eluting with 0 to 10% Ethyl Acetate in hexanes to provide 3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)-benzaldehyde as colorless sheet-like crystals, 475 mg (80%).  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.94 (s, 1H), 7.61 (s, 2H), 6.99 (d,  $J = 2.1$  Hz, 1H), 6.89 (d,  $J = 8.4$  Hz, 1H), 6.59 (m, 1H), 5.15 (s, 2H), 4.05 (s, 2H), 3.37 (s, 3H), 3.25 (m, 1H), 2.31 (s, 6H), 1.14 (d,  $J = 6.0$  Hz, 6H).

Step d:

[1102] To a suspension of  $\text{MgBr}_2$  etherate in THF was added (ethoxy-methyl-phosphinoylmethyl)-phosphonic acid diethyl ester (*Tetrahedron Lett.* 34(10):1585 (1993)). The suspension cleared, and the reaction was allowed to stir for 5 minutes. Triethylamine was then added, followed by a solution of 3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)-benzaldehyde (220 mg) in THF. The reaction was then stirred for 16 h. A saturated solution of ammonium chloride was added, and the solution was diluted with ethyl acetate and water. The layers were separated, and the organic layer was washed with brine and dried ( $\text{Na}_2\text{SO}_4$ ), then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with 80

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to 100% ethyl acetate/hexanes to afford the desired product, ethyl{(E)-2-[3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)phenyl]-ethenyl}-methyl-phosphinate as a colorless oil, 150 mg (51%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.43 (dd, *J* = 17.1 Hz, 1H), 7.29 (s, 1H), 6.9 (m, 2H), 6.6 (m, 1H), 6.25 (dd, *J* = 17.1 Hz, 1H), 5.17, (s, 2H), 4.0 (m, 4H), 3.5 (s, 3H), 3.2 (m, 1H), 2.29 (s, 6H), 1.77 (s, 2H), 1.39 (d, *J* = 14.1 Hz, 3H), 1.34 (t, 3H), 1.14 (d, *J* = 6.0 Hz, 6H).

Step e:

[1103] To a solution of ethyl{(E)-2-[3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)phenyl]-ethenyl}-methyl-phosphinate (150 mg) in methanol was added palladium on carbon (10% wt.) (150 mg). This mixture was stirred under an hydrogen atmosphere (1 atm) for 16 hours, filtered and concentrated under reduced pressure. Subsequent purification by column chromatography on silica gel eluting with 1-2% methanol in dichloromethane yielded the desired product, ethyl{(E)-2-[3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)phenyl]-ethyl}-methylphosphinate ester as a colorless oil, 90 mg (60%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 6.9 (m, 4H), 6.65 (m, 1H), 5.16 (s, 2H), 4.05 (m, 4H), 3.28 (m, 3H), 2.80 (m, 2H), 2.12 (m, 8H), 1.49 (d, *J* = 14.1 Hz, 3H), 1.32 (t, 3H), 1.14 (d, *J* = 6.0 Hz, 6H).

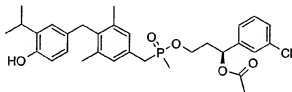
Step f:

[1104] To a solution of ethyl{(E)-2-[3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)phenyl]-ethyl}-methylphosphinate (85 mg) in dichloromethane was added trimethylsilylbromide (0.26 mL, 10 eq). The mixture was stirred 2 hours at room temperature, then evaporated to dryness. The residue was taken up in acetone and treated with water, then concentrated to dryness to yield the title compound as a colorless foam. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.97 (s, 1H), 6.88 (m, 3H), 6.45 (m, 1H), 6.42 (m, 1H), 3.81 (s, 2H), 3.06 (m, 1H), 2.63 (m, 2H), 2.15 (s, 6H), 1.79 (m, 2H), 1.23 (d, *J* = 14.1 Hz, 3H), 1.06 (d, *J* = 6.0 Hz, 6H). LC-MS *m/z* = 361 [C<sub>21</sub>H<sub>29</sub>O<sub>3</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>21</sub>H<sub>29</sub>O<sub>3</sub>P+0.5 H<sub>2</sub>O): C, 68.27; H, 8.18. Found: C,

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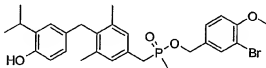
68.12; H, 7.89; HPLC conditions: Column = Waters Atlantis; dC18-150×4.6 mm; Mobile phase = Solvent A: H<sub>2</sub>O/0.05% TFA; Solvent B: ACN/0.05% TFA. Flow rate = 2.0 mL/min; UV@ 254 nm. Retention time in minutes. (rt = 8.13/20.00, 95% purity).

**Compound 97-1:** *S*-3-Acetyl-3-(3-chlorophenyl)propyl[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]methylphosphinate



[1105] The title compound was prepared from [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-methylphosphinic acid (example 72) according to the procedure described for the synthesis of Example Cis-13-1. MP: 52-55 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.32-7.20 (m, 4H), 7.04 (m, 2H), 6.84 (s, 1H), 6.58 (m, 2H), 5.82 (m, 1H), 3.97 (d, *J* = 2.1 Hz, 2H), 4.18-3.85 (m, 2H), 3.25 (m, 1H), 3.18 (d, *J* = 21.0 Hz, 2H), 2.25 (d, *J* = 2.1 Hz, 6H), 2.18 (m, 2H), 2.10 (d, *J* = 1.2 Hz, 3H), 1.69 (m, 2H), 1.47 (dd, *J* = 13.8 Hz, 3H), 1.15 (m, 3H), 1.14 (d, *J* = 7.0 Hz, 6H); LC-MS *m/z* = 557 [C<sub>31</sub>H<sub>38</sub>ClO<sub>5</sub>P]<sup>+</sup>.

**Compound 97-2:** 3-Bromo-4-methoxybenzyl[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-methylphosphinate



[1106] The title compound was prepared from [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-methylphosphinic acid (example 72) according to the procedure described for the synthesis of Example Cis-13-1. MP: 58-61 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.55 (d, *J* = 2.1 Hz, 1H), 7.30 (m, 1H), 6.98 (m, 3H), 6.82 (s, 1H), 6.58 (m, 2H), 6.45 (d, *J* = 2.1 Hz, 1H), 4.94 (s, 2H), 3.96 (s, 2H), 3.86 (s, 3H), 3.25 (m, 1H), 3.23 (d, *J* = 21.0 Hz, 2H), 2.23 (s, 6H), 1.49 (d, *J* = 14.1 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 6H); LC-MS *m/z* = 547

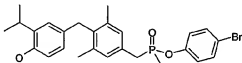
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$[\text{C}_{21}\text{H}_{29}\text{O}_3\text{P} + 2\text{H}]^+$ . Anal. Calcd for  $(\text{C}_{28}\text{H}_{34}\text{BrO}_4\text{P})$ : C, 61.66; H, 6.28. Found: C, 61.93; H, 6.51.

[1107]

## Example 98

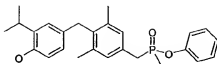
**Compound 98-1:** 4-Bromophenyl [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-methylphosphinate



[1108] To a solution of [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]-methylphosphinic acid (example 72, 0.05 g, 0.144 mmol) in dichloromethane (5 mL), was added oxalyl chloride (0.25  $\mu\text{L}$ , 0.29 mmol) and two drops of dimethyl formamide at 0  $^{\circ}\text{C}$ . Evolution of gas was followed and the reaction mixture was allowed to stir overnight at rt. The volatiles were removed under reduced pressure to give a brown oil. In another flask 4-bromophenol (37 mg, 0.22 mmol) was taken up in 5 mL of dichloromethane followed by addition of triethylamine (61  $\mu\text{L}$ , 0.44 mmol) and cooled to 0  $^{\circ}\text{C}$ . The acid chloride from the first step was taken up in dichloromethane (1 mL) and added to the bromophenol solution. After stirring at rt overnight, the reaction mixture was diluted with dichloromethane and washed with water. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The residue was then purified by medium pressure column chromatography (ISCO), eluted with ethyl acetate-hexanes 50% to 100% ethyl acetate to give the title compound (0.025 g, 0.05 mmol):  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{Cl}$ ):  $\delta$  7.45 (d,  $J = 9.3$  Hz, 2H),  $\delta$  7.11 (d,  $J = 8.1$  Hz, 2H), 6.95 (m,  $J = 8.7$  Hz, 3H), 6.66 (d,  $J = 8.1$  Hz, H), 6.25 (d,  $J = 8.1$  Hz, 1H), 3.97 (s, 2H), 3.27 (d,  $J = 17.7$  Hz, 2H), 3.18 (m, 2H), 2.24 (s, 6H), 1.54 (d,  $J = 13.8$  Hz, 3H), 1.24 (d,  $J = 6.9$  Hz, 6H); LC-MS  $m/z = 501.6$   $[\text{C}_{26}\text{H}_{30}\text{BrO}_3\text{P} + \text{H}]^+$ ; Anal. Calcd for  $(\text{C}_{26}\text{H}_{30}\text{BrO}_3\text{P})$ : C, 62.28; H, 6.03. Found: C, 61.96; H, 5.96.

**Compound 98-2:** Phenyl 3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)-benzyl]methylphosphinate

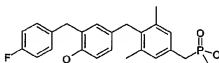
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- [1109] The title compound was prepared from 3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)benzyl]methylphosphinic acid (example 72) according to the procedure described for the synthesis of compound 98-1 (0.030 g, 51 %):  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{Cl}$ ):  $\delta$  7.36-7.29 (m, 2H), 7.22-7.10 (m, 3H), 6.98 (s, 2H), 6.93 (d,  $J = 2.1$  Hz, 1H), 6.63 (d,  $J = 8.4$  Hz, 1H), 6.51-6.47 (dd,  $J = 2.1$ , 8.1 Hz, 1H), 3.95 (s, 2H), 3.20-3.15 (m, 3H), 2.20 (s, 6H), 1.53 (d,  $J = 13.5$  Hz, 3H), 1.23 (d,  $J = 6.9$  Hz, 6H); LC-MS  $m/z = 423.4$  [ $\text{C}_{26}\text{H}_{31}\text{O}_3\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{26}\text{H}_{31}\text{O}_3\text{P} + \text{H}_2\text{O}$ ): C, 70.89; H, 7.55. Found: C, 70.52; H, 7.18.

### Example 99:

**Compound 99:** [3,5-Dimethyl-4-[3'-(4-fluorobenzyl)-4'-hydroxybenzyl]-benzyl]-methylphosphinic acid



Step a:

- [1110] To a stirring solution of 4-bromophenol (8.0 g, 0.5 mmol) in  $\text{ClCH}_2\text{CH}_2\text{Cl}$  (40 mL) at room temperature was added 4-fluorobenzyl alcohol (5.4 mL, 0.5 mmol) and zinc bromide (11.2 g, 0.5 mmol). The mixture was heated to 60 °C for 72 hrs. After cooling to room temperature, water was added. The organic layer was collected and dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by

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medium pressure column chromatography (ISCO) silica gel. Eluting with dichloromethane-hexanes (1:9) to (1:1) afforded 4-bromo-2-(4-fluorobenzyl)-phenol as a white solid (5.3 g, 18.9 mmol, 38%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ): 7.26–7.20 (m, 4H), 7.15 (t, 2H), 6.72 (d, 2H), 5.02 (s, 1H), 3.92 (s, 2H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 50% ethyl acetate in hexanes;  $R_f$  = 0.59.

## Step b:

- [1111] To a stirring solution of 4-bromo-2-(4-fluorobenzyl)-phenol (16 g, 59.9 mmol) in  $\text{CH}_2\text{Cl}_2$  (200 mL) at room temperature was added ethyl-diisopropylamine (15.6 mL, 89.85 mmol) and chloro-methoxy-methane (6.1 mL, 79.67 mmol). The mixture was refluxed for 16 hrs, cooled to room temperature, and water was added. The organic layer was collected, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:9) to afford 4-bromo-2-(4-fluorobenzyl)-1-methoxymethoxybenzene as a light yellow solid (5.3 g, 88%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ): 7.40–6.96 (m, 7H), 5.20 (s, 2H), 3.89 (s, 2H), 3.26 (s, 3H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 6% ethyl acetate in hexanes;  $R_f$  = 0.79.

## Step c:

- [1112] To a stirring solution of 4-bromo-2-(4-fluorobenzyl)-1-methoxymethoxybenzene (6.2 g, 19.93 mmol) in THF (80 mL) at  $-78^\circ\text{C}$  was added *n*-BuLi (8.8 mL, 2.5 M in hexanes). The mixture was stirred at  $-78^\circ\text{C}$  for 1 hr followed by addition of 2,6-dimethyl-4-triisopropylsilyloxybenzaldehyde (6.11 g, 19.93 mmol). The reaction mixture was stirred at  $-78^\circ\text{C}$  for 1 hr, allowed to warm to room temperature and stirred for an additional hour. The reaction mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  and diluted with diethyl ether. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:9) to afford (2,6-dimethyl-4-triisopropylsilyloxy-phenyl)-[3-(4-fluorobenzyl)-

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4-methoxymethoxyphenyl]-methanol as a light yellow oil (8.3 g, 75%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.20–6.88 (m, 7H), 6.47 (s, 2H), 5.97 (d,  $J$  = 4.0 Hz, 1H), 5.65 (d,  $J$  = 4.0 Hz, 1H), 5.14 (s, 2H), 3.85 (s, 2H), 3.25 (s, 3H), 2.11 (s, 6H), 1.24 (m, 3H), 1.08 (d,  $J$  = 7.2 Hz, 18H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 10% ethyl acetate in hexanes;  $R_f$  = 0.47.

Step d:

[1113] To a stirring solution of (2,6-dimethyl-4-triisopropylsilyloxyphenyl)-[3-(4-fluorobenzyl)-4-methoxymethoxyphenyl]-methanol (8.3 g, 15.01 mmol) in  $\text{CH}_2\text{Cl}_2$  (150 mL) at room temperature was added  $\text{Et}_3\text{SiH}$  (9.6 mL, 60.04 mmol) and TFA (4.5 mL, 60.04 mmol). The reaction mixture was stirred at room temperature for 6 hrs. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and saturated  $\text{NaHCO}_3$ . The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. Then to this stirring solution of crude product in  $\text{CH}_2\text{Cl}_2$  (150 mL) at room temperature was added ethyl-diisopropyl-amine (2.6 mL, 15.01 mmol) and chloro-methoxy-methane (1 mL, 13.51 mmol). The mixture was refluxed for 16 hrs, and water was added. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:9) to afford [3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]-phenoxy]-triisopropylsilane as a light yellow oil (7 g, 87%):  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.19–6.66 (m, 7H), 6.54 (s, 2H), 5.12 (s, 2H), 3.82 (s, 4H), 3.25 (s, 3H), 2.11 (s, 6H), 1.23 (m, 3H), 1.06 (d,  $J$  = 7.2 Hz, 18H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:9);  $R_f$  = 0.68.

Step e:

[1114] To a stirring solution of [3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]-phenoxy]-triisopropylsilane (7 g, 13.04 mmol) in THF (100 mL) at room temperature was added tetrabutylammonium fluoride



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(16.3 mL, 1.0 M in THF). The reaction mixture was stirred at room temperature for 2 hr, diluted with diethyl ether and washed with water (30 mL x 2). The organic layer was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (3:7) to afford 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]-phenol as a colorless oil (4.6 g, 93%): <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 6.99 (s, 1H), 7.13 (m, 4H), 6.85 (m, 2H), 6.67 (m, 1H), 6.43 (s, 2H), 5.12 (s, 2H), 3.84 (s, 2H), 3.76 (s, 2H), 3.24 (s, 3H), 2.07 (s, 6H), TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (15:85); R<sub>f</sub> = 0.45.

Step f:

[1115] 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]-phenol (4.6 g, 12.09 mmol) and DMAP (4.4 g, 36.27 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and cooled to 0 °C. Trifluoromethanesulfonyl anhydride (3.1 mL, 18.14 mmol) was slowly added and the reaction mixture was stirred at 0 °C for 2 h. The solution was then quenched with water (60 mL). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (15:85) to afford 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]-phenyltrifluoro-methanesulfonate as a colorless oil (5.8 g, 94%): <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 7.28-6.91 (m, 7H), 6.80 (s, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 5.15 (s, 2H), 3.91 (s, 2H), 3.84 (s, 2H), 3.25 (s, 3H), 2.22 (s, 6H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (15:85); R<sub>f</sub> = 0.65.

Step g:

[1116] To a solution of 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]-phenyltrifluoro-methanesulfonate (5.8 g, 11.32 mmol) in DMF (80 mL) in a bomb apparatus was added MeOH (9.2 mL, 226.4 mmol), Pd(OAc)<sub>2</sub> (0.25 g, 1.13 mmol), DPPP (0.47 g, 1.13 mmol), and

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triethylamine (3.2 mL, 22.64 mmol). 60 PSI of CO was then infused and the reaction mixture was stirred at 90 °C for 16 hrs. The bomb reaction was allowed to cool to 0 °C, CO was vented and the reaction mixture was poured directly into a cold 1 N HCl solution. Ethyl acetate (100 mL x 2) was added and the layers were separated. The combined EtOAc layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (15:85) to afford methyl 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]-benzoate as a colorless oil (4.8 g, 100%): <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 7.64 (s, 2H), 7.28–6.68 (m, 7H), 5.13 (s, 2H), 3.97 (s, 2H), 3.83 (s, 5H), 3.24 (s, 3H), 2.23 (s, 6H). TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (15:75); R<sub>f</sub> = 0.52.

## Step h:

- [1117] To a stirring solution of methyl 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]-benzoate (1.0 g, 2.4 mmol) in THF (12 mL) at 0 °C was added diisobutylaluminum hydride (1.0 M in hexanes, 7.2 mL). The reaction mixture was allowed to come to room temperature and stirred overnight. Water (2 mL) was added followed by 2.4 N HCl until acidic. Ethyl acetate was then added and the organic layer separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]-benzyl alcohol as a light yellow oil (1.0 g, 100%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.19-7.07 (m, 4H), 6.99–6.92 (m, 3H), 6.82–6.78 (m, 2H), 5.15 (s, 2H), 4.64 (s, 2H), 3.98 (s, 2H), 3.95 (s, 3H), 3.94 (s, 2H), 2.25 (s, 6H). TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (4:1); R<sub>f</sub> = 0.35.

## Step i:

- [1118] To a stirring solution of carbon tetrabromide (1.4 g, 4.3 mmol) and triphenyl phosphine (1.1 g, 4.3 mmol) in diethyl ether (10 mL) at 0 °C was added 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]-benzyl

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alcohol (1.0 g, 2.5 mmol) in 5 mL of diethyl ether. The reaction mixture was stirred at room temperature for 16 hrs. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The oil was subjected to medium pressure column chromatography (ISCO), eluting with 20% ethyl acetate-hexanes to 50% ethyl acetate-hexanes to afford 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]-benzyl bromide as a light yellow oil (0.4 g, 35%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.19-7.07 (m, 4H), 6.92-6.99 (m, 3H), 6.82-6.78 (m, 2H), 5.15 (s, 2H), 4.54 (s, 2H), 3.98 (s, 2H), 3.94 (s, 2H), 3.95 (s, 3H), 2.25 (s, 6H).

Step j:

- [1119] A stirring solution of 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]-benzyl bromide (0.25 g, 0.55 mmol) and methyl diethyl phosphite in DMF (3 mL) was heated to 165 °C for 16 h. The reaction mixture was cooled to room temperature and DMF was removed under reduced pressure. The residue was partitioned between water and dichloromethane. The organic layer was separated, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by medium column chromatography (ISCO) on silica gel, eluting with 50% ethyl acetate-hexanes to 100% ethyl acetate to afford ethyl [3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]-benzyl]methylphosphinate as a colorless oil (0.15 g, 56 %):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.19-7.07 (m, 2H), 6.99-6.92 (m, 5H), 6.82-6.78 (m, 2H), 5.15 (s, 2H), 4.19-4.07 (m, 2H), 3.96 (s, 2H), 3.94 (s, 2H), 3.39 (s, 3H), 3.14-3.07 (d,  $J$ =21.0 Hz, 2H), 2.21 (s, 6H), 1.41-1.31 (m, 6H). TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate;  $R_f$ =0.29.

Step k:

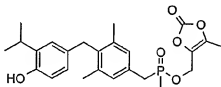
- [1120] The title compound was prepared from ethyl [3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxybenzyl]-benzyl]methylphosphinate

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according to the procedure described for the synthesis of compound 7-14, step b.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ): 7.18–7.10 (m, 2H), 7.00–6.91 (m, 4H), 6.66 (s, 3H), 3.92 (s, 2H), 3.85 (s, 2H), 3.10 (d,  $J = 17.7$  Hz, 2H), 2.20 (s, 6H), 1.38 (d,  $J = 14.1$  Hz, 2H); LC-MS  $m/z = 443$  [ $\text{C}_{25}\text{H}_{28}\text{FO}_4\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{24}\text{H}_{26}\text{FO}_3\text{P} + 1.2 \text{ CH}_2\text{Cl}_2$ ): C, 58.85; H, 5.57. Found: C, 58.82; H, 5.35.

### Example 100

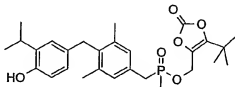
**Compound 100-1:** 5-Methyl-2-oxo-[1,3]dioxol-4-ylmethyl[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]methylphosphinate



[1121] A solution consisting of 3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)benzyl]methylphosphinic acid (compound 72, 61 mg, 0.18 mmol), 4-bromomethyl-5-methyl-[1,3]dioxol-2-one (102 mg, 0.53 mmol) and diisopropylethylamine (0.09 mL, 0.53 mmol) in acetonitrile (2 mL) was stirred at rt for 5 days. The solvent was removed under vacuum and the residue partitioned between EtOAc and 1 N HCl. The organic portion was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum to give a dark oil. Purification of the crude product by preparative HPLC (Waters Atlantis C18 30×150 mm 5 $\mu\text{m}$  column; solvent A: 0.05% TFA/ $\text{H}_2\text{O}$ , solvent B: 0.05% TFA/ACN; gradient from 40% to 100% solvent B over 16 min. Flow rate = 40 mL/min;  $\lambda = 280$  nm, retention time = 9.35/20 min) afforded the titled compound as a white gum upon evaporation of the solvents (13.2 mg, 16%):  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  6.98 (s, 2H), 6.80 (s, 1H), 6.60–6.50 (m, 2H), 4.76 (d,  $J = 9.3$  Hz, 2H), 3.93 (s, 2H), 3.27–3.10 (m, 1H), 3.21 (d,  $J = 16.5$  Hz, 2H), 2.22 (s, 6H), 2.08 (s, 3H), 1.50 (d,  $J = 14.1$  Hz, 3H), 1.11 (d,  $J = 6.9$  Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-methanol (10:1);  $R_f = 0.33$ . HPLC conditions:

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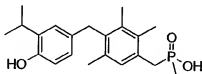
**Compound 100-2:** 5-*tert*-butyl-2-oxo-[1,3]dioxol-4-ylmethyl[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-benzyl]methylphosphinate



[1122] The title compound was prepared from 3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)benzyl]methylphosphinic acid (example 72) according to the procedure described for the synthesis of compound 100-1 (9.7 mg, 9%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.94-6.91 (m, 2H), 6.61-6.49 (m, 2H), 4.82 (ddd,  $J = 7.2$  Hz,  $J = 13.8$  Hz,  $J = 38.7$  Hz, 2H), 3.93 (s, 2H), 3.23-3.11 (m, 1H), 3.14 (d,  $J = 16.8$  Hz, 2H), 1.48 (d,  $J = 13.8$  Hz, 3H), 1.29 (s, 9H), 1.20 (d,  $J = 6.9$  Hz, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  55.84 (s); LC-MS  $m/z = 501$  [ $\text{C}_{28}\text{H}_{37}\text{O}_6\text{P} + \text{H}^+$ ]; TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = ethyl acetate-methanol (10:1);  $R_f = 0.53$ ; retention time = 7.99/20 min.

### Example 101

**Compound 101:** [4-(4'-Hydroxy-3'-isopropylbenzyl)-2,3,5-trimethylbenzyl]methylphosphinic acid



Step a:

[1123] To a stirred solution of 2,3,5-trimethylanisole (5.0 g, 33 mmol) and pyridine (0.7 mL, 0.87 mmol) in dichloromethane (35 mL) at  $0^\circ\text{C}$  was added a solution of  $\text{Br}_2$  (1.7 mL, 33 mmol) in dichloromethane over a 30 min period. The resulting solution was allowed to warm to rt overnight. The reaction mixture was then poured into a cold saturated  $\text{NaHCO}_3$  solution and extracted with dichloromethane. After drying over  $\text{Na}_2\text{SO}_4$ , the organic layer was

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concentrated under reduced pressure to afford crude 4-bromo-2,3,5-trimethylanisole as a semi-solid (7.3 g, 95%):  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  6.84 (s, 1H), 3.75 (s, 3H), 2.33 (s, 3H), 2.31 (s, 3H), 2.11 (s, 3H).

## Step b:

- [1124] A solution of 4-bromo-2,3,5-trimethylanisole (7.3 g, 31.8 mmol) and 48% aqueous HBr (25 ml) in AcOH (25 mL) was refluxed for 4 hrs. The AcOH was removed under vacuum and the aqueous portion extracted with EtOAc. The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with a gradient of hexanes-ethyl acetate (15:1 to 12:1) to afford 4-bromo-2,3,5-trimethylphenol as a grey solid (2.6 g, 38%):  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  9.34 (s, 1H), 6.66 (s, 1H), 2.29 (s, 3H), 2.24 (s, 3H), 2.09 (s, 3H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (4:1);  $R_f$  = 0.5.

## Step c:

- [1125] To a solution of 4-bromo-2,3,5-trimethylphenol (5.33 g, 24.9 mmol) in dichloromethane (100 mL) at 0 °C were added triisopropylsilyl chloride (5.9 mL, 27.4 mL) and TEA (7 mL, 50 mmol). The resulting mixture was allowed to warm to rt overnight. The solution was diluted with dichloromethane, washed with  $\text{NaHCO}_3$ , brine then dried over  $\text{Na}_2\text{SO}_4$  before being concentrated under vacuum. The crude material was purified by column chromatography on silica gel, eluting with hexanes-ethyl acetate (40:1) to afford (4-bromo-2,3,5-trimethylphenoxy)triisopropylsilane as an off-white solid (4.4 g, 48%):  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  6.65 (s, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 2.17 (s, 3H), 1.4-1.2 (m, 3H), 1.08-1.06 (m, 18H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (20:1);  $R_f$  = 0.7.

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Step d:

- [1126] To (4-bromo-2,3,5-trimethylphenoxy)triisopropylsilane (4.4 g, 11.8 mmol) in THF (100 mL) at -78 °C was added a 2.5 M solution of *n*-BuLi in hexanes (5.2 mL, 13 mmol) over a 10 min period. After stirring for 30 min, 3-isopropyl-4-methoxymethoxy benzaldehyde (2.7 g, 13 mmol) in THF (25 mL) was slowly added and the resulting mixture was allowed to warm to rt overnight. The reaction was quenched by adding a saturated solution of NH<sub>4</sub>Cl. After stirring for 5 min, the mixture was diluted with EtOAc, washed with H<sub>2</sub>O, brine and then dried over Na<sub>2</sub>SO<sub>4</sub> before being concentrated under vacuum to afford the crude (3'-isopropyl-4'-methoxymethoxyphenyl)-(2,3,6-trimethyl-4-triisopropylsilyloxyphenyl)methanol as an oil. TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (4:1); product R<sub>f</sub> = 0.48, aldehyde R<sub>f</sub> = 0.42.
- [1127] The crude (3'-isopropyl-4'-methoxymethoxyphenyl)-(2,3,6-trimethyl-4-triisopropylsilyloxyphenyl)methanol was combined with 10% Pd/C (500 mg) in EtOAc (90 mL) and AcOH (10 mL) and stirred at rt under a balloon of H<sub>2</sub> for 18 hrs. The reaction mixture was filtered through a bed of celite®, washed thoroughly with EtOAc and the combined washes concentrated under vacuum to afford crude triisopropyl-[4-(3'-isopropyl-4'-methoxymethoxybenzyl)-2,3,5-trimethylphenoxy]silane as an oil. TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (4:1); R<sub>f</sub> = 0.72.
- [1128] To the crude triisopropyl-[4-(3'-isopropyl-4'-methoxymethoxybenzyl)-2,3,5-trimethylphenoxy]silane in THF (75 mL) was added a 1 M solution of TBAF in THF (12 mL). The greenish brown solution was stirred at rt overnight. Evaporation of the solvent gave crude product as a green oil which was purified by column chromatography on silica gel, eluting with hexanes-ethyl acetate (8:1) to afford [4-(3'-isopropyl-4'-methoxymethoxybenzyl)-2,3,5-trimethylphenol (903 mg): <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 6.91-6.87 (m, 2H), 6.65-6.61 (m, 1H), 6.52 (s, 1H), 5.14 (s, 2H), 3.92 (s, 2H), 3.45 (s, 3H), 3.30-3.2 (m, 1H), 2.16 (s, 3H), 2.15 (s, 3H), 2.11 (s, 3H), 1.17 (d, J = 6.9

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Hz, 6H): TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (8:1);  $R_f$  = 0.14.

Step e:

[1129] To [4-(3'-isopropyl-4'-methoxymethoxybenzyl)-2,3,5-trimethylphenol (549 mg, 1.67 mmol) and pyridine (0.41 mL, 5.01 mmol) in dichloromethane (10 mL) at 0 °C was added triflic anhydride (0.42 mL, 2.51 mmol). After stirring for 2 hrs, the reaction mixture was diluted with dichloromethane, washed with a 1 N solution of HCl, brine and then dried over  $\text{Na}_2\text{SO}_4$  before being concentrated under vacuum to afford crude 4-(3'-isopropyl-4'-methoxymethoxybenzyl)-2,3,5-trimethylphenyltrifluoromethanesulfonate (719 mg, 94%) as an amber-colored oil:  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.11 (s, 1H), 6.98 (d,  $J$  = 2.1 Hz, 1H), 6.89 (d,  $J$  = 8.7 Hz, 1H), 6.57 (dd,  $J$  = 8.7 Hz and  $J$  = 2.1 Hz, 1H), 5.15 (s, 2H), 3.99 (s, 2H), 3.37 (s, 3H), 3.30-3.2 (m, 1H), 2.28 (s, 3H), 2.22 (s, 3H), 2.18 (s, 3H), 1.12 (d,  $J$  = 6.9 Hz, 6H): TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (8:1);  $R_f$  = 0.48.

Step f:

[1130] In a steel bomb, a mixture consisting of 4-(3'-isopropyl-4'-methoxymethoxybenzyl)-2,3,5-trimethylphenyltrifluoromethanesulfonate (719 mg, 1.6 mmol), palladium(II) acetate (35 mg, 0.16 mmol), DPPP (64 mg, 0.16 mmol) and triethylamine (0.44 mL, 3.1 mmol) in DMF (5 mL) and MeOH (5 mL) was heated at 85 °C overnight under 80 psi of CO. The solvents were removed under vacuum and the crude product purified by column chromatography on silica gel, eluting with a gradient of hexanes-ethyl acetate (15:1 to 12:1) to afford methyl [4-(3'-isopropyl-4'-methoxymethoxybenzyl)-2,3,5-trimethylbenzoate (234 mg, 40%):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.49 (s, 1H), 6.96-6.88 (m, 2H), 6.62-6.59 (m, 1H), 5.16 (s, 2H), 4.04 (s, 2H), 3.91 (s, 3H), 3.48 (s, 3H), 3.34-3.25 (m, 1H), 2.46 (s, 3H), 2.27 (s, 3H), 2.19 (s, 3H), 1.19 (d,  $J$  = 6.9 Hz, 6H): TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (8:1);  $R_f$  = 0.33.



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## Step g:

- [1131] To a mixture of methyl[4-(3'-isopropyl-4'-methoxymethoxybenzyl)-2,3,5-trimethylbenzoate (234 mg, 0.63 mmol) in THF (10 mL) at 0 °C was added a solution of DIBAL-H (1.6 mL, 1.6 mmol, 1.0 M solution in THF). The reaction mixture was stirred at rt overnight then quenched with a solution of NaF (265 mg, 6.3 mmol) in H<sub>2</sub>O. After stirring for 30 min, the solution was filtered through a bed of celite® and washed thoroughly with EtOAc. The filtrate was partitioned between EtOAc and H<sub>2</sub>O, washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub> before being concentrated under vacuum to afford crude [4-(3'-isopropyl-4'-methoxymethoxybenzyl)-2,3,5-trimethylbenzyl alcohol (208 mg, 100%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.20 (s, 1H), 7.07 (s, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 6.62 (d, *J* = 8.7 Hz, 1H), 5.15 (s, 2H), 4.71 (s, 2H), 4.02 (s, 2H), 3.48 (s, 3H), 3.34-3.25 (m, 1H), 2.29 (s, 3H), 2.26 (s, 3H), 2.17 (s, 3H), 1.19 (d, *J* = 6.9 Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (4:1); R<sub>f</sub> = 0.21.

## Step h:

- [1132] To a stirred solution of triphenylphosphine (0.76 g, 2.89 mmol) and CBr<sub>4</sub> (0.96 g, 2.89 mmol) in diethyl ether (10 mL) at room temperature was added [4-(3'-isopropyl-4'-methoxymethoxybenzyl)-2,3,5-trimethylbenzyl alcohol (0.58 g, 1.7 mmol). The reaction mixture was stirred at room temperature for 16 h, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with a gradient of ethyl acetate-hexanes (20:1 to 15:1) to afford [4-(3'-isopropyl-4'-methoxymethoxybenzyl)-2,3,5-trimethylbenzyl bromide (0.15 g, 22%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.11 (s, 1H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.56 (dd, *J* = 8.4 Hz, *J* = 2.4 Hz, 1H), 5.15 (s, 2H), 4.72 (s, 2H), 3.95 (s, 2H), 3.36 (s, 3H), 3.22 (m, 1H), 1.15 (d, *J* = 6.9 Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = hexanes-ethyl acetate (9:1); R<sub>f</sub> = 0.42.

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Step i:

[1133] A mixture consisting of [4-(3'-isopropyl-4'-methoxymethoxybenzyl)-2,3,5-trimethylbenzyl bromide (0.15 g, 0.36 mmol) and diethoxymethylphosphine (0.15 mL, 1.1 mmol) in DMF (2 mL) was heated at 130 °C under N<sub>2</sub> for 24 hrs. The solvent was removed under vacuum and the residue purified by preparative TLC (2mm, silica) eluting with ethyl acetate-methanol (8:2) to afford ethyl[4-(3'-isopropyl-4'-methoxymethoxybenzyl)-2,3,5-trimethylbenzyl]methylphosphinate (43 mg, 27%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 6.95 (s, 2H), 6.89 and 6.63 (AB, *J* = 8.7 Hz, 2H), 5.15 (s, 2H), 4.05-3.99 (m, 4H), 3.48 (s, 3H), 3.29 (m, 1H), 3.22 (dd, *J* = 17.7 Hz and *J* = 3.3 Hz, 2H), 2.28 (s, 3H), 2.23 (s, 3H), 2.16 (s, 3H), 1.39 (d, *J* = 13.8 Hz, 3H), 1.30 (t, *J* = 6.9 Hz, 3H), 1.18 (d, *J* = 7.2 Hz, 6H); <sup>31</sup>P (CDCl<sub>3</sub>) δ 52.13 (s); LC-MS *m/z* = 433 [C<sub>25</sub>H<sub>37</sub>O<sub>4</sub>P + H]<sup>+</sup>; TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate; R<sub>f</sub> = 0.19.

Step j:

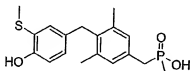
[1134] Bromotrimethylsilane (0.13 mL, 0.99 mmol) was added to a solution of ethyl[4-(3'-isopropyl-4'-methoxymethoxybenzyl)-2,3,5-trimethylbenzyl]methylphosphinate (43 mg, 0.10 mmol) in dichloromethane (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 16 hrs. After removing the solvent under reduced pressure, the residue was treated with acetone-water (6:1, 7 mL) and stirred for 30 min. The solvent was evaporated under vacuum and the residue partitioned between EtOAc/H<sub>2</sub>O. The organic portion was dried over Na<sub>2</sub>SO<sub>4</sub> before being concentrated under vacuum to afford a gummy residue. Dissolution of the residue in ether followed by addition of hexanes and evaporation of the solvents gave the title compound as a white foam (35 mg, 98%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.98 (s, 1H), 6.90-6.86 (m, 2H), 6.60 (d, *J* = 8.4 Hz, 1H), 6.43 (dd, *J* = 8.4 Hz and *J* = 2.4 Hz, 1H), 3.87 (s, 2H), 3.13 (m, 1H), 3.04 (d, *J* = 17.7 Hz, 2H), 2.18 (s, 3H), 2.15 (s, 3H), 2.09 (s, 3H), 1.23 (d, *J* = 14.1 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 6H); <sup>31</sup>P (DMSO-*d*<sub>6</sub>) δ 43.78 (s); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = dichloromethane-methanol-acetic acid (10:1:0.5); R<sub>f</sub> = 0.37;

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LC-MS  $m/z$  = 361  $[\text{C}_{21}\text{H}_{29}\text{O}_3\text{P} + \text{H}]^+$ ; Anal. Calcd for  $(\text{C}_{21}\text{H}_{29}\text{O}_3\text{P} + 0.2 \text{H}_2\text{O})$ : C, 69.29; H, 8.14. Found: C, 69.37, H, 8.47.

### Example 102

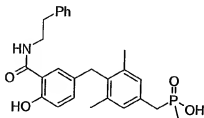
**Compound 102:** [3,5-dimethyl-4-(4'-hydroxy-3'-methylsulfanylbenzyl)-benzyl]-methylphosphinic acid



[1135] The title compound was prepared from 3,5-dimethyl-4-(4'-methoxymethoxy-3'-methylsulfanylbenzyl)-phenol (compound 75, step b) according to the procedure described for the synthesis of compound 101, steps f-j as a light pink solid:  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.58 (s, 1H), 6.94 (s, 2H), 6.78 (d,  $J$  = 2.4 Hz, 1H), 6.65 (d,  $J$  = 8.1 Hz, 1H), 6.52 (dd,  $J$  = 2.4, 8.1 Hz, 1H), 3.87 (s, 2H), 2.93 (d,  $J$  = 17.4 Hz, 2H), 2.25 (s, 3H), 2.16 (s, 6H), 1.19 (d,  $J$  = 13.8 Hz, 3H); MP: 167-169 °C; LC-MS  $m/z$  = 351  $[\text{C}_{18}\text{H}_{23}\text{O}_3\text{PS} + \text{H}]^+$ ; Anal. Calcd for  $(\text{C}_{18}\text{H}_{23}\text{O}_3\text{PS} + 0.7\text{H}_2\text{O})$ : C, 59.55; H, 6.77. Found: C, 59.39; H, 6.47.

### Example 103

**Compound 103:** [3,5-Dimethyl-4-(4'-hydroxy-3'-phenethylcarbamoylbenzyl)-benzyl]-methylphosphinic acid



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## Step a:

- [1136] Methyl 3,5-dimethyl-4-(4'-methoxymethoxy-3'-phenethylcarbamoyl-benzyl)benzoate was prepared from *N*-phenethyl-5-(2,6-dimethyl-4-hydroxybenzyl)-2-methoxymethoxybenzamide (example 37, step c) according to the procedure described for the synthesis of compound 41, steps a-b as a white solid (0.35 g, 84%):  $^1\text{H NMR}$  (300 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  8.16 (t,  $J = 5.4$  Hz, 1H), 7.69 (s, 2H), 7.20–7.40 (m, 6H), 7.09 (m, 2H), 5.17 (s, 2H), 4.04 (s, 2H), 3.85 (s, 3H), 3.52 (m, 2H), 3.30 (s, 3H), 2.82 (t,  $J = 7.2$  Hz, 2H), 2.27 (s, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = 40% ethyl acetate in hexanes;  $R_f = 0.51$ .

## Step b:

- [1137] To a refluxing mixture of methyl 3,5-dimethyl-4-(4'-methoxymethoxy-3'-phenethylcarbamoyl-benzyl)benzoate (1.1 g, 2.38 mmol) and  $\text{LiBH}_4$  (0.33 g, 15 mmol) in THF (60 mL) was added MeOH (2.2 mL, 52.5 mmol) over two hours. Then the reaction mixture was refluxed for another 2 hrs. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to afford 5-(4-hydroxymethyl-2,6-dimethyl-benzyl)-2-methoxymethoxy-*N*-phenethyl-benzamide as a white foam (1 g, 97%):  $^1\text{H NMR}$  (300 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  8.16 (t,  $J = 5.4$  Hz, 1H), 7.20–7.40 (m, 6H), 7.08 (s, 2H), 7.02 (s, 2H), 5.17 (s, 2H), 5.08 (t,  $J = 6.0$  Hz, 1H), 4.44 (d,  $J = 6.0$  Hz, 2H), 3.95 (s, 2H), 3.52 (m, 2H), 3.30 (s, 3H), 2.82 (t,  $J = 7.2$  Hz, 2H), 2.19 (s, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (4:6);  $R_f = 0.38$ .

## Step c:

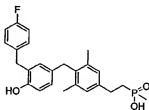
- [1138] The title compound was prepared from 5-(4-hydroxymethyl-2,6-dimethyl-benzyl)-2-methoxymethoxy-*N*-phenethyl-benzamide by the procedure described for the synthesis of compound 101, steps h-j as a light yellow foam:  $^1\text{H NMR}$  (300 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  12.05 (s, 1H), 8.81 (t,  $J = 5.4$  Hz, 1H), 7.65 (d,  $J = 2.1$  Hz, 1H), 7.28 (m, 5H), 6.96 (d,  $J = 1.8$  Hz, 2H), 6.81

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(m, 2H), 3.90 (s, 2H), 3.51 (m, 2H), 2.95 (d,  $J = 17.7$  Hz, 2H), 2.84 (t,  $J = 7.2$  Hz, 2H), 2.19 (s, 6H), 1.23 (d,  $J = 13.8$  Hz, 3H); LC-MS  $m/z = 452$  [ $C_{26}H_{30}NO_4P + H$ ] $^+$ ; Anal. Calcd for ( $C_{26}H_{30}NO_4P + 0.6TFA + 0.7H_2O$ ): C, 61.35; H, 6.06; N, 2.63. Found: C, 61.05; H, 5.82; N, 2.70.

### Example 104

**Compound 104:** [2-(3,5-Dimethyl-4-[3'-(4-fluorobenzyl)-4'-hydroxybenzyl]phenyl)ethyl]methylphosphinic acid



Step a:

[1139] Dimethyl 2-(3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-hydroxybenzyl]-phenyl)ethylphosphonate was prepared from methyl 3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-methoxymethoxy-benzyl]-benzoate (compound 99, step g) according to the procedure described for the synthesis of compound 42-1 as a colorless oil:  $^1H$  NMR (200 MHz,  $DMSO-d_6$ ):  $\delta$  6.81–7.22 (m, 8H), 6.69 (m, 1H), 5.12 (s, 2H), 3.84 (s, 4H), 3.62 (d,  $J = 10.6$  Hz, 6H), 3.24 (s, 3H), 2.65 (m, 2H), 2.14 (s, 6H), 2.02 (m, 2H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate;  $R_f = 0.49$ .

Step b:

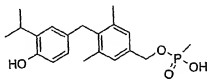
[1140] The title compound was prepared from dimethyl 2-(3,5-dimethyl-4-[3'-(4-fluorobenzyl)-4'-hydroxybenzyl]phenyl)ethylphosphonate according to the procedure described for the synthesis of compound 70 as a light pink foam;  $^1H$  NMR (300 MHz,  $DMSO-d_6$ ):  $\delta$  9.19 (s, 1H), 7.01–7.22 (m, 4H), 6.89 (s, 2H), 6.72 (d,  $J = 2.1$  Hz, 1H), 6.66 (d,  $J = 8.1$  Hz, 1H), 6.55 (dd,  $J = 2.1, 8.1$  Hz, 1H), 3.79 (s, 2H), 3.77 (s, 2H), 2.67 (m, 2H), 2.14 (s, 6H), 1.88 (m, 2H), 1.28 (d,  $J = 13.8$  Hz, 3H); LC-MS  $m/z = 427$  [ $C_{25}H_{28}FO_3P + H$ ] $^+$ ; Anal.

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Calcd for  $(C_{25}H_{28}FO_3P + 1.1H_2O + 0.3HBr)$ : C, 63.81; H, 6.53. Found: C, 63.54; H, 6.30.

### Example 105

**Compound 105-1:** Methylphosphonic acid 3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)benzyl ester



#### Step a

[1141] A mixture of methyl-3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)benzoate (Example 24-1, 1.52 g, 4.26 mmol) in methanol (8.0 mL) and 4 N HCl-dioxane (3.2 mL, 12.8 mmol) was heated at 100 °C for 5 min in a microwave oven. The solvent was removed under reduced pressure and the residue was dissolved in THF (25.0 mL). The solution was cooled to 0 °C and to it was slowly added DIBAL (14.7 mL, 14.7 mmol). The reaction mixture was stirred at 0 °C for 2 h, quenched with saturated sodium potassium tartrate and diluted with hexanes (20 mL). The reaction mixture was stirred at room temperature for 2 h and the organic layer was separated. The organic solution was dried over  $MgSO_4$ , filtered and concentrated under reduced pressure to afford 3,5-dimethyl-4-(4'-hydroxy 3'-isopropyl-benzyl)benzyl alcohol (1.01 g, 83%) as white solid:  $^1H$  NMR (300 MHz,  $CD_3OD$ ):  $\delta$  7.05 (s, 2H), 6.84 (d,  $J$  = 2.1 Hz, 1H), 6.58 (m, 2H), 4.55 (s, 2H), 3.96 (s, 2H), 3.22 (m, 1H), 2.25 (s, 6H), 1.14 (d,  $J$  = 7.0 Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethyl acetate-hexanes (1:3);  $R_f$  = 0.4.

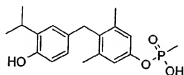
#### Step b

[1142] To a solution of 3,5-dimethyl-4-(4'-hydroxy-3'-isopropyl-benzyl)benzyl alcohol (0.13 g, 0.46 mmol), methylphosphonic acid (0.04 g,

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0.38 mmol) and pyridine (0.11 mL) in DMF (3.5 mL) at room temperature was slowly added EDCI (0.18 g, 0.91 mmol). The reaction mixture was stirred at 70 °C for 24 h and allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with 20% methanol in dichloromethane to afford the title compound (0.04 g, 24%) as a white solid: MP: 125-127 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.09 (s, 2H), 6.83 (d, *J* = 2.1 Hz, 1H), 6.56 (m, 2H), 4.87 (d, *J* = 6.9 Hz, 1H), 3.96 (s, 2H), 3.21 (m, 1H), 2.24 (s, 6H), 1.30 (d, *J* = 17.7 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 6H); LC-MS *m/z* = 361 [C<sub>20</sub>H<sub>27</sub>O<sub>4</sub>P-H]<sup>+</sup>.

**Compound 105-2:** Methylphosphonic acid 3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)phenyl ester



#### Step a

[1143] To a solution of 3,5-dimethyl-4-(3-isopropyl-4-methoxymethoxybenzyl)phenol (Chiellini *et al.*, *Bioorg. Med. Chem. Lett.* 10:2607 (2000), 0.30 g, 0.95 mmol) in methanol (6.0 mL) was added 2 N HCl (1.4 mL, 2.8 mmol). The reaction mixture was stirred at room temperature for 72 h, diluted with water (15 mL) and extracted with ethyl acetate (10 mL). The organic solution was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to afford 3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)phenol (0.23 g, 89%) as colorless oil: <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 6.84 (d, *J* = 2.1 Hz, 1H), 6.58 (m, 2H), 6.53 (s, 2H), 3.87 (s, 2H), 3.23 (m, 1H), 2.17 (s, 6H), 1.15 (d, *J* = 7.0 Hz, 6H); TLC conditions: Uniplate silica gel, 250 microns; Mobile phase = acetone-hexanes (1:3); R<sub>f</sub> = 0.5.

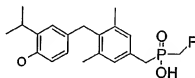
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Step b

- [1144] The title compound was prepared from 3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)phenol according to the procedure described for the synthesis of compound 105-1. MP: 53-56 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 6.91 (s, 2H), 6.84 (d, *J* = 2.1 Hz, 1H), 6.54 (m, 2H), 3.96 (s, 2H), 3.21 (m, 1H), 2.24 (s, 6H), 1.59 (d, *J* = 17.7 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 6H); LC-MS *m/z* = 349 [C<sub>19</sub>H<sub>25</sub>O<sub>4</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>19</sub>H<sub>25</sub>O<sub>4</sub>P): C, 65.51; H, 7.23. Found: C, 65.23; H, 7.47.

## Example 106

**Compound 106:** [3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)benzyl]-(fluoromethyl)-phosphinic acid



Step a:

- [1145] 3,5-Dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)benzyl bromide (example 68, step a, 1.84 g, 4.70 mmol), was dissolved in 20mL THF and cooled to -78 °C. LDA (2.64 mL, 5.17 mmol, 2.0 M in heptane/THF/ethyl benzene) was added dropwise, followed by ethyl(1,1-diethoxyethyl)phosphinate (1.11 g, 5.17 mmol), which was prepared according to the procedure given by EP 0307362B1. The reaction mixture was allowed to stir for 16 h, warmed to room temperature, then quenched with a saturated solution of NH<sub>4</sub>Cl (aq.), and extracted into ethyl acetate. The organic layer was rinsed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to a yellow oil, which was purified by column chromatography on silica gel, eluting with a gradient of hexanes-acetone (19:1) to afford ethyl [3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)benzyl]-(1,1-diethoxyethyl)phosphinate (1.39 g, 56.7%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):



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$\delta$  6.93 (s, 2H), 6.90 (s, 1H), 6.87 (d,  $J = 8.4$  Hz, 1H), 6.62 (d,  $J = 8.4$  Hz, 1H), 5.13, (s, 2H), 3.90 (m, 4H), 3.53 (m, 4H), 3.35 (s, 3H), 3.19 (m, 1H), 3.08 (d,  $J = 14.4$  Hz, 2H), 2.15 (s, 6H), 1.39 (d,  $J = 11.1$  Hz, 3H), 1.08 (m, 15H);  $^{31}\text{P}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  43.526 (s, 1P).

Step b:

[1146] Ethyl [3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)-benzyl]-(1,1-diethoxyethyl)phosphinate (1.53 g, 2.94 mmol) was taken up in dichloromethane-ethanol [10:1] (50 mL) and cooled to 0 °C. Chlorotrimethylsilane (0.56 mL, 4.41 mmol) was added dropwise, and the reaction mixture was allowed to stir for 60 h at 0 °C. The solution was concentrated under reduced pressure to a colorless oil which was purified by column chromatography on silica gel in acetone-hexanes (1:9 to 1:1) to afford ethyl [3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)benzyl]-phosphinate (0.39 g, 32.4 %):  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  6.94 (d,  $J = 546$  Hz, 1H), 6.93 (s, 3H), 6.87 (d,  $J = 8.4$  Hz, 1H), 6.60 (d,  $J = 8.4$  Hz, 1H), 5.12, (s, 2H), 3.99 (m, 2H), 3.93 (s, 2H), 3.34 (s, 3H), 3.19 (m, 1H), 3.17 (d,  $J = 18.0$  Hz, 2H), 2.15 (s, 6H), 1.18 (t, 3H), 1.10 (d,  $J = 6.9$  Hz, 6H);  $^{31}\text{P}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  36.356 (s, 1P).

Step c:

[1147] Ethyl [3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)-benzyl]-phosphinate (0.39 g, 0.95 mmol) was dissolved in dichloromethane (4.0 mL) with triethylamine (0.13 mL, 0.95 mmol) and paraformaldehyde (0.39 g). The reaction mixture was heated at 130 °C for 1 h, and the resulting oil was partitioned in dichloromethane (10 mL) and water (10 mL). The organic layer was rinsed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to a colorless oil, which was purified by column chromatography on silica gel with acetone-hexanes (4:6 to 8:2) to afford ethyl [3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)-benzyl]-(hydroxymethyl)-phosphinate (0.28 g, 67.1%) as a colorless oil:  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  6.93 (s, 3H), 6.87 (d,  $J = 8.4$  Hz, 1H), 6.60 (d,

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$J = 8.4$  Hz, 1H), 5.44, (m, 1H), 5.12 (s, 2H), 3.91 (m, 2H), 3.88 (s, 2H), 3.34 (s, 3H), 3.19 (m, 1H), 3.05 (m, 2H), 2.10 (s, 6H), 1.14 (t, 3H), 1.10 (d,  $J = 7.2$  Hz, 6H);  $^{31}\text{P}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  48.524 (s, 1P).

Step d:

[1148] Ethyl [3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)-benzyl]-(hydroxymethyl)-phosphinate (0.19 g, 0.44 mmol) was dissolved in dichloromethane and cooled to  $-78^\circ\text{C}$  before the addition of DAST (0.21 mL, 0.88 mmol). The reaction was allowed to warm to room temperature. After stirring at rt for 16 h, the reaction mixture was quenched with a solution of saturated  $\text{NaHCO}_3$  (aq.), and extracted into dichloromethane. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give a colorless oil which was purified by column chromatography on silica gel, eluting in acetone-hexanes (1:19 to 4:6) to afford ethyl [3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)benzyl]-(fluoromethyl)-phosphinate (76.2 mg, 39.5 %) as a colorless oil:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.26 (s, 2H), 7.00 (s, 1H), 6.90 (d,  $J = 8.7$  Hz, 1H), 6.63 (d,  $J = 7.8$  Hz, 1H), 5.15, (s, 2H), 4.67 (s, 1H), 4.51 (s, 1H), 4.15 (m, 2H), 3.95 (s, 2H), 3.47 (s, 3H), 3.26 (m, 1H), 3.24 (d,  $J = 18.3$ , 2H), 2.23 (s, 6H), 1.34 (t, 3H), 1.18 (d,  $J = 6.9$  Hz, 6H);  $^{31}\text{P}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  43.06 (d,  $J = 140.7$ , 1P).

Step e:

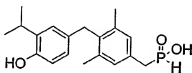
[1149] Ethyl [3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)-benzyl]-(fluoromethyl)-phosphinate (76.2 mg, 0.18 mmol) was cooled to  $-78^\circ\text{C}$  and bromotrimethylsilane (0.23 mL, 1.80 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature over 16 h, and was concentrated to an oil under reduced pressure. The oil was taken up in acetonitrile-water (1:1, 10 mL) and sonicated for 1 m, then concentrated under reduced pressure to dryness. The solid was dissolved in  $\text{Et}_2\text{O}$  (10 mL), and extracted into 1 N  $\text{NaOH}$  (30 mL). The aqueous layer was acidified to pH 1 with concentrated  $\text{HCl}$  (1.0 mL), and the product was back extracted into  $\text{Et}_2\text{O}$  (30 mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated

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under reduced pressure to a yellow solid, which was purified by preparative HPLC on a C18 column, to afford the title compound (19.0 mg, 29.9%). MP 132-134°C;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  8.98 (s, 1H), 6.91 (s, 2H), 6.84 (s, 1H), 6.60 (d,  $J$  = 7.8 Hz, 1H), 6.46 (d,  $J$  = 8.1 Hz, 1H), 4.62 (s, 1H), 4.47 (s, 1H), 3.83 (s, 2H), 3.13 (m, 1H), 3.06 (d,  $J$  = 16.8, 2H), 2.15 (s, 6H), 1.09 (d,  $J$  = 7.2 Hz, 6H);  $^{31}\text{P}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  33.22 (d,  $J$  = 140.7, 1P); LC-MS  $m/z$  = 365.3 [ $\text{C}_{20}\text{H}_{26}\text{FO}_3\text{P} + \text{H}$ ] $^+$ ; Anal. Calcd for ( $\text{C}_{20}\text{H}_{26}\text{FO}_3\text{P} + 1.7\text{eq H}_2\text{O}$ ): C, 60.81; H, 7.50; Found: C, 60.8; H, 5.14.

### Example 107

**Compound 107:** [3,5-Dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)benzyl]-phosphinic acid



Step a:

[1150] Ethyl [3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)-benzyl]-(1,1-diethoxyethyl)phosphinate (compound 106, step a, 300 g, 0.576 mmol) was taken up in dichloromethane-ethanol [10:1] (6 mL) and cooled to 0°C. Chlorotrimethylsilane (0.147 mL, 1.15 mmol) was added dropwise, and the reaction mixture was sealed and placed into a refrigerator for 60 hrs at 4°C. The solution was concentrated under reduced pressure to a colorless oil which was purified by preparatory thin-layer chromatography on silica gel, eluting with acetone-hexanes (3:7) to afford ethyl [3,5-dimethyl-4-(3'-isopropyl-4'-hydroxybenzyl)benzyl]-phosphinate (0.135 g, 65 %).  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  9.03 (s, 1H), 6.98 (d,  $J$  = 543 Hz, 1H), 6.95 (m, 2H), 6.85 (m, 1H), 6.64 (m, 1H), 6.50 (m, 1H), 4.06-4.00 (m, 2H), 3.86 (s, 2H), 3.81 (s, 2H), 3.21-3.14 (d,  $J$  = 35.0 Hz, 1H), 3.20 (m, 1H), 2.19 (s, 6H), 1.20 (m, 3H), 1.10 (d,  $J$  = 7.5 Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = acetone-hexanes (1:1);  $R_f$  = 0.20.

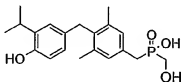
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Step b:

[1151] Ethyl [3,5-dimethyl-4-(3'-isopropyl-4'-hydroxybenzyl)benzyl]-phosphinate (85 mg, 0.24 mmol) was cooled to -30 °C and bromotrimethylsilane (0.31 mL, 2.36 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature over 16 h and was concentrated to an oil under reduced pressure. The oil was taken up in acetonitrile-water (5:1), stirred for 30 min at 30 °C, then concentrated under reduced pressure to dryness. The solid was dissolved in acetone, coevaporated, redissolved in acetone and filtered through a PTFE syringe filter into a tared 4 mL vial. The acetone was then evaporated and the solid triturated with hexane to afford the title compound (70.0 mg, 89%): MP: 98-101 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.01 (d, *J* = 549 Hz, 1H), 7.00 (m, 2H), 6.87 (m, 1H), 6.61 (d, *J* = 15.0 Hz, 1H), 6.55 (m, 2H), 3.96 (s, 2H), 3.17 (m, 1H), 3.16 (d, *J* = 15.0, 2H), 2.25 (s, 6H), 1.17 (d, *J* = 7.0 Hz, 6H; LC-MS *m/z* = 333 [C<sub>19</sub>H<sub>25</sub>O<sub>3</sub>P+H]<sup>+</sup>; Anal. Calcd for (C<sub>19</sub>H<sub>25</sub>O<sub>3</sub>P + 0.5 H<sub>2</sub>O + 0.1 CH<sub>3</sub>COCH<sub>3</sub>): C, 66.77; H, 7.72; Found: C, 66.65; H, 7.81.

## Example 108

**Compound 108:** [3,5-Dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)benzyl]-(hydroxymethyl)phosphinic acid



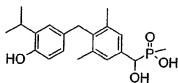
[1152] Ethyl [3,5-dimethyl-4-(3'-isopropyl-4'-hydroxybenzyl)benzyl]-(hydroxymethyl)-phosphinate (compound 106, step c, 55 mg, 0.14 mmol) was cooled to -30 °C and bromotrimethylsilane (0.19 mL, 1.41 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature over 16 h and was concentrated to an oil under reduced pressure. The oil was taken up in acetonitrile-water (4:1), stirred for 30 m at 30 °C, then concentrated under reduced pressure to dryness. The solid was dissolved in

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acetone and filtered through a PTFE filter into a 4 mL vial. The acetone was then evaporated and the solid triturated with hexane to afford the title compound as an oil (45.0 mg, 88%).  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  7.00 (m, 2H), 6.82 (m, 1H), 6.54 (m, 2H), 3.91 (s, 2H), 3.67 (d,  $J$  = 5.0, 2H), 3.16 (d,  $J$  = 18.0, 2H), 3.20 (m, 1H), 2.19 (s, 6H), 1.12 (d,  $J$  = 7.0 Hz, 6H); LC-MS  $m/z$  = 363  $[\text{C}_{20}\text{H}_{27}\text{O}_4\text{P} + \text{H}]^+$ ; Anal. Calcd for  $(\text{C}_{20}\text{H}_{27}\text{O}_4\text{P} + 2.0 \text{ H}_2\text{O})$ : C, 60.29; H, 7.84; Found: C, 59.99; H, 7.12.

## Example 109

**Compound 109:** [Hydroxy-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-phenyl]-methyl]-methyl-phosphinic acid



Step a:

[1153] [3,5-Dimethyl-4-(3'-isopropyl-4'-methoxymethoxy-benzyl)-phenyl]-methanol (intermediate for compound 68, step a, 1.00 g, 3.04 mmol) was dissolved in dichloromethane and cooled to 0 °C before the addition of Dess-Martin periodinane (9.51 mL, 4.57 mmol, 0.48 M solution in DCM). The reaction was allowed to warm to room temperature, stirred for 1 h and the solvent removed. The crude product was diluted with  $\text{Et}_2\text{O}$  and 1:1 sat.  $\text{NaHCO}_3/\text{Na}_2\text{S}_2\text{O}_3$ , stirred until biphasic, then the layers were partitioned and the organic layer was concentrated. The crude product was purified by column chromatography on silica gel, eluting with a gradient of hexanes-acetone (5:1) to afford 3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxy-benzyl)benzaldehyde (0.96g, 97%).  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  9.94 (s, 1H), 7.62 (s, 2H), 6.99 (m, 1H), 6.92 (d,  $J$  = 9.0 Hz, 1H), 6.63 (m, 1H), 5.17 (s, 2H), 4.04 (m, 2H), 3.38 (s, 3H), 3.23 (m, 1H), 2.32 (s, 6H), 1.15 (d,  $J$  = 6.9 Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = ethylacetate-hexanes (1:5);  $R_f$  = 0.66.

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## Step b:

[1154] Methyl-phosphinic acid propyl ester (0.086 mL, 0.674 mmol, prepared from n-propanol using the procedure described in *Zh. Obshch. Khim.*, 31:179-184 (1961)) was dissolved in 5 mL THF and cooled to -78 °C. LDA (0.34 mL, 0.674 mmol, 2.0 M in heptane/THF/ethyl benzene) was added dropwise and stirring continued 30 min at -78 °C at which time 3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxy-benzyl)benzaldehyde (0.20 g, 0.61 mmol) dissolved in 2 mL THF was added. The reaction mixture was allowed to stir for 40 min then quenched with a saturated solution of NH<sub>4</sub>Cl (aq.) and extracted into Et<sub>2</sub>O. The layers were partitioned and the organics were concentrated. The crude product was purified by column chromatography on silica gel, eluting with acetone-hexanes (3:7) to afford propyl[hydroxy-[3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxy-benzyl)-phenyl]-methyl]-methyl-phosphinate (0.100 g, 36 %). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.10 (m, 2H), 6.90-6.86 (m, 2H), 6.63 (d, 1H), 6.16 (m, 1H), 5.15, (s, 2H), 4.79, (s, 1H), 3.93 (m, 2H), 3.73-3.62 (m, 2H), 3.37 (s, 3H), 3.23 (m, 1H), 3.08 (d, *J* = 14.4 Hz, 2H), 2.13 (s, 6H), 1.48 (m, 2H), 1.31 (d, *J* = 17 Hz, 3H), 1.15 (m, 6H), 0.77 (t, 3H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = acetone-hexanes (3:2); R<sub>f</sub> = 0.28.

## Step c:

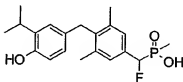
[1155] Propyl[hydroxy-[3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxy-benzyl)-phenyl]-methyl]-methyl-phosphinate (100 mg, 0.22 mmol) was cooled to -30 °C and bromotrimethylsilane (0.29 mL, 2.23 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature over 16 h and was concentrated to an oil under reduced pressure. The oil was taken up in acetonitrile-water (4:1), stirred for 30 min at 30 °C, then concentrated under reduced pressure to dryness. The crude product was coevaporated with CH<sub>3</sub>CN and concentrated to a foam. The solid was dissolved in acetone and filtered through a PTFE filter into a 4 mL vial. The acetone was then evaporated and the solid triturated with hexane to afford the title compound as an oil (60.0 mg, 74%). MP: 71-74 °C; <sup>1</sup>H NMR (300 MHz,

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CD<sub>3</sub>OD):  $\delta$  7.05 (m, 2H), 6.72 (m, 1H), 6.43 (m, 2H), 4.70 (d,  $J = 9.5$ , 2H) 3.84 (s, 2H), 3.15 (m, 1H), 2.14 (s, 6H), 1.30 (d,  $J = 14.0$  Hz, 3H), 1.02 (d,  $J = 7.5$  Hz, 6H); LC-MS  $m/z = 363$  [C<sub>20</sub>H<sub>27</sub>O<sub>4</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>20</sub>H<sub>27</sub>O<sub>4</sub>P + 0.5 H<sub>2</sub>O + 0.25 CH<sub>3</sub>COCH<sub>3</sub>): C, 64.58; H, 7.70; Found: C, 64.72; H, 7.58.

### Example 110

**Compound 110:** [Fluoro-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-phenyl]-methyl]-methyl-phosphinic acid



Step a:

[1156] Propyl[hydroxy-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-phenyl]-methyl]-methyl-phosphinate (example 109, step b, 0.12 g, 0.27 mmol) was dissolved in dichloromethane and cooled to 0 °C before the addition of DAST (0.03 mL, 0.27 mmol). The reaction was stirred at 0 °C for 70 min, then quenched with a saturated solution of NaHCO<sub>3</sub>. The mixture was diluted with ethyl acetate and H<sub>2</sub>O and the layers were partitioned. The organic layer was concentrated under reduced pressure and the crude product was purified by preparatory thin-layer chromatography on silica gel, eluting with acetone-hexanes (7:13) to afford propyl[fluoro-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-phenyl]-methyl]-methyl-phosphinate (80 mg, 66 %). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  7.13 (s, 2H), 6.95-6.88 (m, 2H), 6.65-6.61 (m, 1H), 6.02 (s, 0.5H), 5.78, (s, 0.5H), 5.16, (s, 2H), 3.97 (s, 2H), 3.90-3.80 (s, 2H), 3.37 (s, 3H), 3.26 (m, 1H), 2.23 (s, 6H), 1.57-1.49 (m, 2H), 1.49 (d,  $J = 15.0$  Hz, 3H), 1.11 (m, 6H), 0.87 (t, 3H); TLC conditions: Uniplat silica gel, 250 microns; Mobile phase = acetone-hexanes (1:1); R<sub>f</sub> = 0.63.

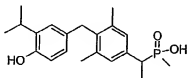
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Step b:

[1157] Propyl[fluoro-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-phenyl]-methyl]-methyl-phosphinate (100 mg, 0.22 mmol) was cooled to -30 °C and bromotrimethylsilane (0.29 mL, 2.23 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature over 16 h and was concentrated to an oil under reduced pressure. The oil was taken up in acetonitrile-water (5:1), stirred for 30 min at 30 °C, then concentrated under reduced pressure to dryness. The solid was dissolved in acetone and filtered through a PTFE filter into a 4 mL vial. The acetone was then evaporated and the material was dissolved in EtOAc and washed twice with H<sub>2</sub>O. The solid was triturated with hexanes to afford the title compound (45.0 mg, 79%). MP 78-81 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.17 (s, 2H), 6.88 (m, 1H), 6.59-6.55 (m, 2H), 4.00 (s, 2H), 3.23 (m, 1H), 2.29 (s, 6H), 1.52 (d, *J* = 15.0 Hz, 3H), 1.17 (d, *J* = 7.5 Hz, 6H); LC-MS *m/z* = 365 [C<sub>20</sub>H<sub>26</sub>FO<sub>4</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>20</sub>H<sub>26</sub>FO<sub>4</sub>P + 0.4 H<sub>2</sub>O + 0.1 CH<sub>3</sub>COCH<sub>3</sub>): C, 64.60; H, 7.32; Found: C, 64.78; H, 7.38.

## Example 111

**Compound 111:** [1-(3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)-phenyl)ethyl]-methylphosphinic acid



Step a:

[1158] To a stirred solution of 3,5-dimethyl-4-[(4'-*O*-methoxymethoxy-3'-*iso*-propylbenzyl)]benzaldehyde (compound 109, step a, 0.5 g, 1.53 mmol) in THF (15 mL) at 0 °C was added MeMgBr (1.0 mL, 3.06 mmol, 3.0 M solution in THF). The reaction mixture was stirred at rt for 3 h, quenched with saturated aqueous NH<sub>4</sub>Cl solution (20 mL) and stirred for 10 min. The



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reaction mixture was extracted with ethyl acetate (2x50 mL) and the combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:4) to afford

1-[3,5-dimethyl-4-(4'-*O*-methoxymethoxy-3'-*iso*-propylbenzyl)phenyl]ethyl alcohol (0.39 g, 75%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.09 (s, 2H), 7.0 (d,  $J = 2.4$  Hz, 1H), 6.90 (d,  $J = 8.4$  Hz, 1H), 6.65 (dd,  $J = 2.1, 8.4$  Hz, 1H), 5.18 (s, 2H), 4.87 (q,  $J = 6.6$  Hz, 1H), 4.0 (s, 2H), 3.50 (s, 3H), 3.34-3.30 (m, 1H), 2.29 (s, 6H), 1.53 (d,  $J = 6.0$  Hz, 3H), 1.21 (d,  $J = 6.6$  Hz, 6H); TLC conditions: Uniplate silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (2:3);  $R_f = 0.4$ .

Step b:

[1159] To a stirred solution of 1-[3,5-dimethyl-4-(4'-*O*-methoxymethoxy-3'-*iso*-propylbenzyl)phenyl]ethyl alcohol (0.28 g, 0.81 mmol) in ether (10 mL) at 0 °C was added phosphorous tribromide (0.28 g, 1.05 mmol). The reaction mixture was stirred at 0 °C for 2 h, quenched with ice (10 g) and stirred at 0 °C for 10 min. The reaction mixture was extracted with ether (100 mL) and washed with brine. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:4) to afford 1-[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenyl]-bromoethane (0.20 g, 70%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.09 (s, 2H), 7.03 (d,  $J = 12.0$  Hz, 2H), 6.59 (dd,  $J = 5.4, 7.5$  Hz, 1H), 4.90 (q,  $J = 6.6$  Hz, 1H), 3.99 (s, 2H), 3.28-3.15 (m, 1H), 2.29 (s, 6H), 1.54 (d,  $J = 6.0$  Hz, 3H), 1.26 (d,  $J = 6.9$  Hz, 6H); TLC conditions: Uniplate silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (2:8);  $R_f = 0.75$ .

Step c:

[1160] A stirring solution of 1-[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenyl]bromoethane (125 mg, 0.92 mmol) and methyl diethylphosphite (0.5 mL) in DMF (2.0 mL) was heated at 70 °C for 8 h. The

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reaction mixture was cooled to room temperature and the volatiles removed under reduced pressure. The residue was extracted with ethyl acetate (2x50 mL) and washed with brine. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by medium pressure column chromatography (ISCO) on silica gel, eluting with 50% ethyl acetate-hexanes to afford ethyl [1-(3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenyl)ethyl]-methylphosphinate as a colorless oil (13 mg, 10%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.02 (s, 2H), 6.94-6.90 (m, 1H), 6.61 (dd,  $J$ =3.0, 8.1 Hz, 1H), 6.58-6.55 (m, 1H), 4.11-4.09 (m, 2H), 3.95 (s, 2H), 3.28-3.20 (m, 1H), 2.20 (s, 6H), 1.64-1.36 (m, 6H), 1.20 (dd,  $J$ =2.2, 6.6 Hz, 6H); TLC conditions: Uniplate silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (3:2);  $R_f$ = 0.35.

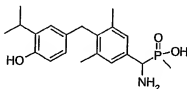
Step d:

[1161] To a stirred solution of ethyl [1-(3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)phenyl)ethyl]-methylphosphinate (70 mg, 0.17 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) at 0 °C was added TMSBr (0.28 g, 0.3 mL, 1.8 mmol). The reaction mixture was stirred at 0 °C for 30 min, allowed to warm to rt and stirred for 16 h. The solvent was removed under reduced pressure and the residue was dissolved in  $\text{CH}_3\text{OH}$  (3 mL) and the solvent was removed under reduced pressure. The residue was triturated with acetonitrile (3 mL) and purified by HPLC to afford the title compound as a white solid (20 mg, 32%, MP 87-90 °C, 100% pure).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.06 (s, 2H), 6.84 (d,  $J$ =2.4 Hz, 1H), 6.59 (dd,  $J$ =8.1, 15.3 Hz, 2H), 3.96 (s, 2H), 3.33-3.20 (m, 1H), 3.18-3.10 (m, 1H), 2.25 (s, 6H), 1.56 (dd,  $J$ =7.5, 16.8 Hz, 3H), 1.28 (d,  $J$ =13.8 Hz, 3H), 1.14 (d,  $J$ =7.9 Hz, 6H); LC-MS  $m/z$  = 361 [ $\text{C}_{21}\text{H}_{29}\text{O}_3\text{P}+\text{H}$ ] $^+$ ; HPLC conditions: Zorbax-SB-Aq-4.6x250 nm column; mobile phase =  $\text{CH}_3\text{OH}$ :TFA (7:3) flow rate = 1.0 mL/min; detection = UV 220, 254, 280 nm retention time in min: 9.97; Anal. Calcd: (MF: $\text{C}_{21}\text{H}_{29}\text{O}_3\text{P}+1.0 \text{ H}_2\text{O}$ ) Calcd: C:66.65, H:8.26 Found: C: 66.61, H:7.93.

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## Example 112

**Compound 112:** [Amino-(3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylbenzyl)-phenyl)methyl]-methyl-phosphinic acid



Step a:

[1162] To a stirred solution of 3,5-dimethyl-4-(4'-*O*-methoxymethoxy-3'-*iso*-propylbenzyl)benzaldehyde (compound 109, step a, 0.35 g, 1.0 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (10 mL) at room temperature were added 4-methoxybenzylamine (0.17 g, 1.2 mmol) and  $\text{MgSO}_4$  (0.35 g, 4.0 mmol). The reaction mixture was stirred at rt for 16 h, filtered, washed with  $\text{CH}_2\text{Cl}_2$  (50 mL) and concentrated. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate-hexanes (1:4) to afford [3,5-dimethyl-4-(4'-*O*-methoxymethyl-3'-*iso*-propylbenzyl)benzyl]-*N*-(4-methoxybenzyl)imine as a viscous oil (0.35 g, 74%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.2 (s, 1H), 7.38 (s, 2H), 7.19-7.14 (m, 2H), 6.85-6.78 (m, 3H), 6.57 (dd,  $J$  = 3.6, 8.4 Hz, 1H), 5.07 (s, 2H), 4.68 (s, 2H), 3.92 (s, 2H), 3.73 (s, 3H), 3.39 (s, 3H), 3.23-3.18 (m, 1H), 2.19 (s, 6H), 1.08 (d,  $J$  = 6.9 Hz, 6H); TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (1:4);  $R_f$  = 0.5.

Step b:

[1163] A stirred solution of [3,5-dimethyl-4-(4'-*O*-methoxymethyl-3'-*iso*-propylbenzyl)benzyl]-*N*-(4-methoxybenzyl)imine (0.35 g, 0.78 mmol) and propyloxymethylphosphite (120 mg, 0.98 mmol) in toluene (10 mL) was heated at 70 °C under  $\text{N}_2$  for 36 h. The solvent was removed under vacuum and the residue purified by column chromatography (silica gel) eluting with ethyl acetate-hexane (30-50%) to afford propyl[*N*-(4-methoxybenzylamino-

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(3,5-dimethyl-4-(4'-*O*-methoxymethyl-3'-*iso*-propylbenzyl)-phenyl)methyl]-methylphosphinate (290 mg, 65%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.23 (d, *J* = 8.7 Hz, 2H), 7.13 (s, 2H), 6.95-6.87 (m, 4H), 6.69 (d, *J* = 8.4 Hz, 1H), 5.18 (s, 2H), 4.08-3.88 (m, 4H), 4.01 (s, 2H), 3.83 (s, 3H), 3.59-3.51 (m, 1H), 3.50 (s, 3H), 3.33-3.29 (m, 1H), 2.29 (s, 3H), 1.56-1.49 (m, 2H), 1.48-1.45 (m, 2H), 1.34 (d, *J* = 14.1 Hz, 3H) 1.18 (d, *J* = 6.9 Hz, 6H), 0.97 (t, *J* = 7.5 Hz, 3H); TLC conditions: Uniplat silica gel, 250 microns; mobile phase = ethyl acetate-hexanes (3:2); R<sub>f</sub> = 0.3.

Step c:

[1164] A mixture of propyl [*N*-4-methoxybenzylamino-(3,5-dimethyl-4-(4'-*O*-methoxymethyl-3'-*iso*-propylbenzyl)-phenyl)methyl]-methylphosphinate (0.275 g, 0.48 mmol) and 10% Pd(OH)<sub>2</sub> (100 mg) in MeOH (25 mL) was stirred under 50 psi of H<sub>2</sub> for 6 hrs. The reaction mixture was filtered through a bed of celite®, washed thoroughly with EtOAc and the combined washes concentrated under vacuum to afford propyl[amino-(3,5-dimethyl-4-(4'-*O*-methoxymethyl-3'-*iso*-propylbenzyl)-phenyl)methyl]-methylphosphinate (200 mg, 89%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.68 (s, 1H), 7.24 (d, *J* = 6.0 Hz, 1H), 6.95-6.90 (m, 2H), 6.66-6.63 (m, 1H), 5.17 (s, 2H), 4.05-3.95 (m, 5H), 3.50 (s, 3H), 3.31-3.23 (m, 1H), 2.28 (s, 6H), 1.85-1.65 (m, 4H), 1.41-1.29 (m, 3H), 1.19-1.15 (m, 6H), 0.97 (t, *J* = 5.4 Hz, 3H); Uniplat silica gel, 250 microns; Mobile phase = CH<sub>2</sub>Cl<sub>2</sub>/MeOH (4:1); R<sub>f</sub> = 0.42.

Step d:

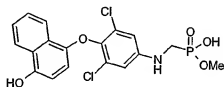
[1165] To a solution of propyl[amino-(3,5-dimethyl-4-(4'-*O*-methoxymethyl-3'-*iso*-propylbenzyl)-phenyl)methyl]-methylphosphinate (0.2 g, 0.44 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4.0 mL) at 0 °C was added bromotrimethylsilane (0.68 g, 4.4 mmol). The reaction mixture was stirred at room temperature for 16 h and the solvent was removed under reduced pressure. The residue was treated with methanol and water (4:1, 5.0 mL) and the solvents were removed under reduced pressure. The residue was treated with acetonitrile and filtered to afford the title compound as a white solid (140 mg, 87%). MP 132 -134 °C;

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$^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.22 (s, 2H), 6.84 (s, 1H), 6.58 (dd,  $J = 2.7$ , 4.5 Hz, 2H), 4.35 (d,  $J = 12.3$  Hz, 1H), 4.0 (s, 2H), 3.31-3.20 (m, 1H), 2.31 (s, 6H), 1.26 (d,  $J = 14.7$  Hz, 3H), 1.13 (d,  $J = 6.9$  Hz, 6H); LC-MS  $m/z = 362$  [ $\text{C}_{20}\text{H}_{28}\text{NO}_3\text{P}^+$ ]; HPLC conditions: Zorbax-SB-Aq-4.6x250 nm column; mobile phase =  $\text{CH}_3\text{OH}:\text{TFA}$  (7:3) flow rate = 1.0 mL/min; detection = UV 220, 254, 280 nm retention time in min: 11.75; Anal. Calcd for ( $\text{C}_{20}\text{H}_{28}\text{NO}_3\text{P} + 1.0 \text{ TFA} + 1.0 \text{ H}_2\text{O}$ ): C, 53.55; H, 6.33; N, 2.84. Found: C, 53.21; H, 6.62; N, 3.0.

### Example 113

**Compound 113:** 3,5-Dichloro-4-(4'-hydroxynaphthoxy)phenylaminomethyl-phosphonic acid monomethyl ester



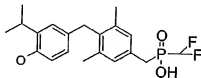
[1166] To a stirred solution of dimethyl-*N*-*t*-butoxycarbonyl-[3,5-dichloro-4-(4'-*O*-methoxynaphthoxy)phenylamino]methylphosphonate, prepared according to the procedure described for the synthesis of compound 90, step d, (220 mg, 0.48 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at  $-78^\circ\text{C}$  was added  $\text{BBr}_3$  (0.3 g, 1.4 mmol). The reaction mixture was allowed to warm to rt and stirred for 14 h and poured into ice water (100 mL) and stirred for 1 h. The reaction mixture was extracted with ethyl acetate (2x50 mL). The combined organic layers were washed with water and brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Crude dimethyl 3,5-dichloro-4-(4'-hydroxynaphthoxy)phenylaminomethyl phosphonate (140 mg, 0.3 mmol) was dissolved in *tert*-butylamine (11.4 mL, 11.4 mmol) and the reaction mixture was heated at  $70^\circ\text{C}$  for 12 h. The solvent was removed under reduced pressure and the crude residue was purified by preparative HPLC to afford the title compound (20 mg, 34%, MP:  $85\text{--}87^\circ\text{C}$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  8.33 (dd,  $J = 0.9$ , 7.5 Hz, 1H), 8.22 (dd,  $J = 0.9$ , 7.5 Hz, 1H), 7.56-7.51 (m,

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2H), 6.86 (s, 2H), 6.59 (d,  $J = 7.8$  Hz, 1H), 6.21 (d,  $J = 8.1$  Hz, 1H), 3.72 (d,  $J = 10.5$  Hz, 3H), 3.44 (d,  $J = 12.3$  Hz, 2H); LC-MS  $m/z = 428$   $[C_{18}H_{16}Cl_2NO_5P+H]^+$ ; HPLC conditions: Agilent Zorbax SB-Aq-3.0  $\times 150$  mm column; mobile phase =  $CH_3OH:TFA$  (7:3) flow rate = 1.0 mL/min; detection = UV 220, 254, 280 nm retention time in min: 9.01; Anal. Calcd: (MF:  $C_{18}H_{16}Cl_2NO_5P + 0.35$   $t\text{-BuNH}_2 + 0.64$  TFA) Calcd: C:47.15, H:3.92, N:3.59 Found: C: 46.86, H:4.23, N:4.04.

### Example 114

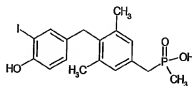
**Compound 114:** (Difluoromethyl)-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)benzyl]-phosphinic acid



- [1167] Ethyl [3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)-benzyl]-phosphinate is alkylated with iododifluoromethane, as described in Froestl, *et. al*, *J. Med. Chem.* 38:3297 (1995). The resulting ethyl (difluoromethyl)-[3,5-dimethyl-4-(3'-isopropyl-4'-methoxymethoxybenzyl)-benzyl]-phosphinate is then deprotected as described for compound 106, step e to give (difluoromethyl)-[3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)benzyl]-phosphinic acid.

### Example 115

**Compound 115:** [3,5-Dimethyl-4-(4'-hydroxy-3'-iodo-benzyl)benzyl]-methylphosphinic acid



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## Step a:

- [1168] Triisopropylsilyl chloride (5.8 mL, 27.06 mmol) was added to a heterogeneous mixture of 4-hydroxybenzaldehyde (3 g, 24.6 mmol) and triethylamine (6.9 mL, 49.2 mmol) in dichloromethane (150 mL) at rt. After stirring at rt for 3 h, the clear solution was quenched with methanol and stirred at rt for 5 min. The reaction mixture was diluted with ethyl acetate and washed with water (2X), brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel 95/5 to 90/10 hexanes/ethyl acetate) to afford 4-triisopropylsilyloxy-benzaldehyde (6.5 g, 95%) as an oil.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  9.92 (s, 1H), 7.82 (d,  $J$  = 8.1 Hz, 2H), 7.01 (d,  $J$  = 8.1 Hz, 2H), 1.40-1.25 (m, 3H), 1.14 (d,  $J$  = 7.2 Hz, 18H).  $R_f$  = 0.75 hexanes/ethyl acetate 80/20.

## Step b:

- [1169] A solution of *s*-BuLi (39 mL, 54.1 mmol, 1.4 M in cyclohexane) was added to a solution of 4-bromo-3,5-dimethyl-phenol (5.19 g, 25.83 mmol) in THF (150 mL) at -78 °C. The yellow solution was stirred at -78 °C for 15 minutes and a solution of 4-triisopropylsilyloxy-benzaldehyde (6.85 g, 24.6 mmol) in THF (150 mL) was cannulated in. After stirring at -78 °C for 15 min, the clear pale yellow solution was quenched with acetic acid (5.9 mL, 98.4 mmol), warmed to -20 °C, diluted with water and extracted with ethyl acetate (2X). The organics were washed with a saturated solution of  $\text{NaHCO}_3$ , brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (90/10 to 70/30 hexanes/ethyl acetate) to afford (2,6-dimethyl-4-hydroxyphenyl)-(4-triisopropylsilyloxy-phenyl)methanol (4.61 g, 47%).  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.07 (s, 1H), 7.05 (d,  $J$  = 8.7 Hz, 2H), 6.77 (d,  $J$  = 8.7 Hz, 2H), 6.38 (s, 2H), 6.00 (d,  $J$  = 3.9 Hz, 1H), 5.52 (d,  $J$  = 3.9 Hz, 1H), 2.11 (s, 6H), 1.30-1.15 (m, 3H), 1.05 (d,  $J$  = 6.9 Hz, 18H).  $R_f$  = 0.2 hexanes/ethyl acetate 80/20.

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## Step c:

- [1170] A degassed mixture of (2,6-dimethyl-4-hydroxyphenyl)-(4-triisopropylsilyloxy-phenyl)methanol (4.61 g), Pd(OH)<sub>2</sub>/C (20%, 500 mg), acetic acid (10 mL) and ethyl acetate (90 mL) was shaken under 60 Psi of hydrogen at rt. After shaking at rt for 24 h, the catalyst was filtered off over Celite® and the black cake rinsed with ethyl acetate. The combined filtrates were diluted with ethyl acetate and washed with water (2X), a saturated solution of NaHCO<sub>3</sub>, brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (90/10 to 80/20 hexanes/ethyl acetate) to afford 3,5-dimethyl-4-(4'-triisopropylsilyloxy-benzyl)phenol (4.3 g, 97%). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.29 (s, 1H), 6.86 (d, *J* = 8.1 Hz, 2H), 6.77 (d, *J* = 8.1 Hz, 2H), 6.58 (s, 2H), 3.91 (s, 2H), 2.20 (s, 6H), 1.30-1.15 (m, 3H), 1.10 (d, *J* = 6.9 Hz, 18H). R<sub>f</sub> = 0.6 hexanes/ethyl acetate 70/30.

## Step d:

- [1171] 3,5-Dimethyl-4-(4'-triisopropylsilyloxy-benzyl)phenol was transformed into ethyl [3,5-dimethyl-4-(4'-triisopropylsilyloxy-benzyl)benzyl]-methyl-phosphinate according to the procedure described for the synthesis of example 99, steps f-j. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.97 (s, 2H), 6.84 (d, *J* = 8.1 Hz, 2H), 6.77 (d, *J* = 8.1 Hz, 2H), 4.20-4.00 (m, 2H), 3.96 (s, 2H), 3.13 (d, *J* = 15.9 Hz, 2H), 2.24 (s, 6H), 1.43 (d, *J* = 13.8 Hz, 3H), 1.34 (t, *J* = 6.9 Hz, 3H), 1.30-1.15 (m, 3H), 1.10 (d, *J* = 6.9 Hz, 18H). R<sub>f</sub> = 0.25 dichloromethane/methanol 95/5.

## Step e:

- [1172] A solution of tetrabutylammonium fluoride (9.5 mL, 9.5 mmol, 1 M in THF) was added to a solution of ethyl[3,5-dimethyl-4-(4'-triisopropylsilyloxy-benzyl)benzyl]-methyl-phosphinate (3.1 g, 6.3 mmol) in THF (50 mL) at rt. After stirring at rt for 1 h, the reaction mixture was diluted with ethyl acetate and washed with water then brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The off white solid was taken up in dichloromethane,



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sonicated for 1 min and collected by filtration to afford ethyl[3,5-dimethyl-4-(4'-hydroxy-benzyl)benzyl]-methyl-phosphinate (1.99 g, 95%). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 9.15 (s, 1H), 6.95 (s, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.65 (d, *J* = 8.7 Hz, 2H), 4.00-3.90 (m, 2H), 3.86 (s, 2H), 3.08 (d, *J* = 17.7 Hz, 2H), 2.17 (s, 6H), 1.33 (d, *J* = 14.1 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 3H). R<sub>f</sub> = 0.45 dichloromethane/methanol 90/10.

Step f:

[1173] A solution of N-iodosuccinimide in DMF (1 mL) was added to a solution of ethyl[3,5-dimethyl-4-(4'-hydroxy-benzyl)benzyl]-methyl-phosphinate (670 mg) in DMF (5 mL) at rt. After stirring at rt for 10 min, the reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography (dichloromethane/methanol 95/5) to afford ethyl[3,5-dimethyl-4-(4'-hydroxy-3'-iodo-benzyl)benzyl]-methyl-phosphinate (350 mg, 38%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.28 (s, 1H), 6.90 (s, 2H), 6.71 (s, 2H), 4.10-3.90 (m, 2H), 3.86 (s, 2H), 3.05 (d, *J* = 17.7 Hz, 2H), 2.17 (s, 6H), 1.37 (d, *J* = 13.8 Hz, 3H), 1.28 (t, *J* = 6.9 Hz, 3H); LC-MS *m/z* = 459 [C<sub>19</sub>H<sub>24</sub>IO<sub>3</sub>P + H]<sup>+</sup>. R<sub>f</sub> = 0.30 dichloromethane/methanol 95/5.

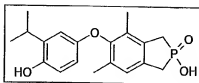
Step g:

[1174] The title compound was prepared from ethyl[3,5-dimethyl-4-(4'-hydroxy-3'-iodo-benzyl)benzyl]-methyl-phosphinate according to the procedure described for the synthesis of compound 7-14, step b as a white solid (230 mg, 70%). MP 223-224 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.26 (s, 1H), 6.95 (s, 2H), 6.78 (s, 2H), 3.86 (s, 2H), 2.95 (d, *J* = 17.7 Hz, 2H), 2.16 (s, 6H), 1.23 (d, *J* = 14.1 Hz, 3H); LC-MS *m/z* = 431 [C<sub>17</sub>H<sub>20</sub>O<sub>3</sub>P + H]<sup>+</sup>; Anal. Calcd for (C<sub>17</sub>H<sub>20</sub>O<sub>3</sub>P): C, 47.46; H, 4.69. Found: C, 47.44; H, 4.41.

### Example 116

**Compound 116:** 2,3-Dihydro-4,6-dimethyl-5-(4'-hydroxy-3'-isopropylphenoxy)-2-oxo-1H-2λ<sup>5</sup>-isophosphindol-2-ol

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Step a:

- [1175] Diethyl 3,5-dimethyl-4-hydroxy-phthalate was synthesized from diethyl butyromediate and (E,Z)-1 methoxy-2-methyl-3-trimethylsilyloxy-1,3-pentadiene according to the procedure described by Danishefsky *et al.*, *J. Am. Chem. Soc.* 101:7001-7008 (1979) (3.31 g, 51%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.71 (s, 1H), 5.45 (br s, 1H), 4.45 (q, *J* = 6.9 Hz, 2H), 4.33 (q, *J* = 6.9 Hz, 2H), 2.29 (s, 3H), 2.22 (s, 3H), 1.41 (t, *J* = 6.9 Hz, 3H), 1.38 (t, *J* = 6.9 Hz, 3H).

Step b:

- [1176] An heterogeneous mixture of diethyl-3,5-dimethyl-4-hydroxy-phthalate (1 g, 3.8 mmol), bis-(3-isopropyl-4-methoxy)-iodonium tetrafluoroborate (2.09 g, 4.94 mmol), copper powder (473 mg, 7.6 mmol) and triethylamine (0.79 mL, 5.7 mmol) in dichloromethane (40 mL) was stirred in the dark at rt. After stirring at rt in the dark for 2 days, the insolubles were filtered off through Celite® and rinsed with dichloromethane. The combined filtrates were concentrated under reduced pressure and the residue purified by flash column chromatography (dichloromethane/hexanes 50/50 to 100/0) to afford diethyl-3,5-dimethyl-4-(3'-isopropyl-4'-methoxy-phenoxy)-phthalate (1.065 g, 68%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.81 (s, 1H), 6.84 (d, *J* = 3.3 Hz, 1H), 6.70 (d, *J* = 9.0 Hz, 1H), 6.35 (dd, *J* = 9.0, 3.3 Hz, 1H), 4.45 (q, *J* = 6.9 Hz, 2H), 4.39 (q, *J* = 6.9 Hz, 2H), 3.81 (s, 3H), 3.31 (heptuplet, *J* = 6.9 Hz, 1H), 2.20 (s, 3H), 2.16 (s, 3H), 1.42 (t, *J* = 6.9 Hz, 6H), 1.22 (d, *J* = 6.9 Hz, 6H). R<sub>f</sub> = 0.50 hexanes/ethyl acetate 80/20.

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## Step c:

- [1177] A solution of diisobutylaluminum hydride (12.8 mL, 12.8 mmol, 1 M in dichloromethane) was added to a solution of diethyl-3,5-dimethyl-4-(3'-isopropyl-4'methoxy-phenoxy)-phthalate (1.065 g, 2.6 mmol) in dichloromethane (30 mL) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was quenched at 0 °C by adding ethyl acetate. The solution was poured into a 1 N aqueous solution of HCl (75 mL) and diluted with ethyl acetate. The layers were separated and the organics were washed with a 1 N aqueous solution of HCl (2X), brine, a saturated solution of NaHCO<sub>3</sub>, brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/ethyl acetate 50/50 to 0/100) to afford 3,5-dimethyl-2-hydroxymethyl-4-(3'-isopropyl-4'methoxy-phenoxy)benzyl alcohol (751 mg, 88%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.13 (s, 1H), 6.84 (d, *J* = 3.0 Hz, 1H), 6.68 (d, *J* = 8.7 Hz, 1H), 6.33 (dd, *J* = 8.7, 3.0 Hz, 1H), 4.83 (s, 2H), 4.80 (s, 2H), 3.80 (s, 3H), 3.31 (heptuplet, *J* = 6.9 Hz, 1H), 2.28 (s, 3H), 2.16 (s, 3H), 1.22 (d, *J* = 6.9 Hz, 6H). *R*<sub>f</sub> = 0.15 hexanes/ethyl acetate 50/50.

## Step d:

- [1178] Triphenylphosphine (2.1 g, 8.1 mmol) was added to a solution of carbon tetrabromide (2.65 g, 8.1 mmol) in ether (25 mL) at rt. The white heterogeneous mixture was stirred at rt for 5 minutes and a solution of 3,5-dimethyl-2-hydroxymethyl-4-(3'-isopropyl-4'methoxy-phenoxy)benzyl alcohol (751 mg, 2.3 mmol) in ether (10 mL) was cannulated in. After stirring at rt for 18 h, the insolubles were filtered off and rinsed with ether. The combined filtrates were concentrated under reduced pressure and the residue was purified by flash column chromatography (dichloromethane/hexanes 5/95 to 30/70) to afford 2-bromomethyl-3,5-dimethyl-4-(3'-isopropyl-4'methoxy-phenoxy)benzyl bromide (624 mg, 60%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.16 (s, 1H), 6.81 (d, *J* = 3.0 Hz, 1H), 6.69 (d, *J* = 9.0 Hz, 1H), 6.32 (dd, *J* = 9.0, 3.0 Hz, 1H), 4.74 (s, 2H), 4.67 (s, 2H), 3.80 (s, 3H), 3.31 (heptuplet, *J* = 6.9

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Hz, 1H), 2.23 (s, 3H), 2.14 (s, 3H), 1.21 (d,  $J = 6.9$  Hz, 6H).  $R_f = 0.55$  hexanes/ethyl acetate 90/10.

Step e:

[1179] A mixture of 2-bromomethyl-3,5-dimethyl-4-(3'-isopropyl-4'-methoxy-phenoxy)benzyl bromide (1.146 g, 2.5 mmol),  $H_2PO_2NH_4$  (1.1 g, 12.5 mmol), hexamethyldisilazane (5.4 mL, 25 mmol) in mesitylene (30 mL) was heated at 170 °C for 18 h. After cooling, the insolubles were filtered off through Celite® and rinsed with methanol. The combined filtrates were extracted with a 1 N solution of NaOH (2X). The combined aqueous extracts were acidified to pH 1 with conc. HCl and extracted with ethyl acetate (2X), dried ( $Na_2SO_4$ ) and concentrated under reduced pressure. The residue was purified by flash column chromatography (acetonitrile/methanol 10/90 to 80/20) to afford 2,3-dihydro-4,6-dimethyl-5-(3'-isopropyl-4'-methoxy-phenoxy)-2-oxo-1H-2 $\lambda^5$ -isophosphindol-2-ol (438 mg, 49%).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.02 (s, 1H), 6.81 (d,  $J = 3.0$  Hz, 1H), 6.68 (d,  $J = 9.0$  Hz, 1H), 6.32 (dd,  $J = 9.0$ , 3.0 Hz, 1H), 3.80 (s, 3H), 3.30 (heptuplet,  $J = 6.9$  Hz, 1H), 3.22 (d,  $J = 14.1$  Hz, 2H), 3.11 (d,  $J = 14.4$  Hz, 2H), 2.13 (s, 3H), 2.07 (s, 3H), 1.21 (d,  $J = 6.9$  Hz, 6H).  $R_f = 0.25$  acetonitrile/methanol 60/40.

Step f:

[1180] A solution of boron tribromide (6 mL, 6.1 mmol, 1 M in dichloromethane) was added to a solution of 2,3-dihydro-4,6-dimethyl-5-(3'-isopropyl-4'-methoxy-phenoxy)-2-oxo-1H-2 $\lambda^5$ -isophosphindol-2-ol (438 mg, 1.22 mmol) in dichloromethane (12 mL) at rt. After stirring at rt for 18 h, the tan reaction mixture was quenched by adding ice crystals and extracted with ethyl acetate (2X). The combined organic extracts were dried ( $Na_2SO_4$ ) and concentrated under reduced pressure. The residue was purified by preparative HPLC on an Agilent Zorbax 19x150 mm C18 5  $\mu m$  (acetonitrile + 0.1% TFA/water + 0.1% TFA 10/90 to 70/30 in 15 min)  $rt = 10.2$  min to afford the title compound (438 mg, 49%).  $^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  8.93 (br s, 1H), 7.06 (s, 1H), 6.69 (d,  $J = 3.0$  Hz, 1H), 6.64 (d,  $J = 8.7$  Hz, 1H),

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6.16 (dd,  $J = 8.7, 3.0$  Hz, 1H), 3.16 (heptuplet,  $J = 6.9$  Hz, 1H), 3.00 (d,  $J = 13.5$  Hz, 2H), 2.90 (d,  $J = 13.5$  Hz, 2H), 2.03 (s, 3H), 1.99 (s, 3H), 1.13 (d,  $J = 6.9$  Hz, 6H). LC-MS  $m/z = 347$  [ $C_{19}H_{23}O_4P + H$ ]<sup>+</sup>.

- [1181] For all chemical structures pictured herein, when an oxygen is depicted with only a single bond to another atom, the presence of a hydrogen bonded to the oxygen is to be assumed. When a nitrogen is depicted with only two bonds to one or more other atoms, the presence of a hydrogen bonded to the nitrogen is to be assumed.

**CH<sub>2</sub>Cl<sub>2</sub>: dichloromethane**

**DMF: dimethylformamide**

**TEA: triethylamine**

**THF: tetrahydrofuran**

**TFA: trifluoroacetic acid**

**MgSO<sub>4</sub>: magnesium sulfate**

**TBSCl: *t*-butyldimethylsilyl chloride**

**H<sub>2</sub>O: water**

**DMSO: dimethyl sulfoxide**

**CH<sub>3</sub>CN: acetonitrile**

- [1182] Examples of use of the method of the invention includes the following.

It will be understood that these examples are exemplary and that the method of the invention is not limited solely to these examples.

- [1183] For the purposes of clarity and brevity, chemical compounds are referred to by their synthetic example numbers in the biological examples below.

### Example A: Receptor Binding

- [1184] The purpose of these studies was to determine the affinity of T3 and various thyromimetics for human thyroid hormone receptors TR $\alpha$ 1 and TR $\beta$ 1.

- [1185] *Methods:* Baculoviruses expressing TR $\alpha$ 1, TR $\beta$ 1 and RXR $\alpha$  were generated using cDNA and other reagents from Invitrogen (Carlsbad, CA). To

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produce TR/RXR heterodimer proteins, the sf9 insect cells were first grown to a density of  $1.5 \times 10^5$  cells/ mL. TR $\alpha$ 1 or TR $\beta$ 1 and RXR $\alpha$  baculovirus stocks were added to the cell culture with a ratio of 1 to 1 (multiplicity of infection =10). The cells were harvested three days after the infection. The cells were lysed in assay buffer (50 mM NaCl, 10% Glycerol, 20 mM tris, pH 7.6 2 mM EDTA, 5 mM  $\beta$ -mercaptoethanol and 1.25% CHAPS) and the lysates were assayed for T3 binding as follows:  $^{125}$ I-T3 was incubated with the lysates of TR and RXR recombinant baculoviruses coinfecting cells (50  $\mu$ l) in assay buffer for one h and then the  $^{125}$ I-T3-TR/RXR complex was separated from free  $^{125}$ I-T3 by a mini-gel-filtration (Sephadex G50) column. The bound  $^{125}$ I-T3 was counted with a scintillation counter.

[1186] Binding of compounds to either the TR $\alpha$ 1 or TR $\beta$ 1 were also performed by means of scintillation proximity assays (SPA). The SPA assay, a common method used for the quantitation of receptor-ligand equilibria, makes use of special beads coated with a scintillant and a capture molecule, copper, which binds to the histidine-tagged  $\alpha$  or  $\beta$  receptor. When labeled T3 is mixed with receptor and the SPA beads, radioactive counts are observed only when the complex of protein and radiolabeled ligand is captured on the surface of the bead. Displacement curves were also generated with labeled T3 and increasing concentrations of unlabeled thyromimetics of interest.

[1187] *Results:* Examples of representative T3 binding results using the gel filtration method are shown in Figure 1(a). SPA assay results for T3 are shown in Figures 1(b) and 1(c). Table 3 below shows the SPA data generated with various thyromimetics of interest. Binding results for T3 demonstrated a  $K_d=0.29$ nM for TR $\alpha$  and a  $K_d=0.67$ nM for TR $\beta$ .

TABLE 3

Compound	Ki TR $\alpha$ (nM)	Ki TR $\beta$ (nM)
17	1.21	0.29
1	285	36.1
12-1	1666	662
3	46	5.42
6	16	26
9	350	204
11	121	30.3

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Compound	Ki TR $\alpha$ (nM)	Ki TR $\beta$ (nM)
13-1- <i>cis</i>	2583	1979
13-1- <i>trans</i>	1744	1322
13-6- <i>cis</i>	4710	3589
13-2- <i>cis</i>	488	419
13-2- <i>trans</i>	1354	469
13-3- <i>cis</i>	2837	3431
13-3- <i>trans</i>	2006	2456
13-6- <i>trans</i>	1526	1574
13-5- <i>trans</i>	354	281
13-5- <i>cis</i>	4432	1008
13-7- <i>trans</i>	1554	3798
13-4- <i>trans</i>	2129	1815
13-4- <i>cis</i>	5531	1521
13-7- <i>cis</i>	49632	45135
7	58	3.3
2	1416	271
4	14.1	0.99
5	1.84	0.84
8	3.74	0.97
10	>2000	>2000
8-1	18.6	2.51
15-3	>2000	>2000
19	304	52
8-2	114	20
24-1	378	31
7-5	67	9.5
25	>2000	363
22	186	31
21	>1400	>180
7-6	98	7.6
24-2	>2000	24
26	594	87
19-2	343	20
7-4	>2000	>2000
30	>2000	>2000
23	>2000	>2000
19-3	1760	128
28	375	14.0
20	>2000	>2000
7-3	31	6.6
7-2	>2000	146
29	661	47
7-1	1166	106
32	284	96
24	>2000	>2000
27	>2000	>2000
31	540	73
24-3	113	2.87

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Compound	Ki TR $\alpha$ (nM)	Ki TR $\beta$ (nM)
33	267	16.7
34	118	6.5
41-2	>2000	>2000
38	254	5.4
42-2	>2000	>2000
39	>2000	58
7-7	898	90
41-3	>2000	280
24-4	>2000	92
7-8	62	9.7
42	794	16.2
40	30	1.1
7-14	429	52
7-9	110	5.4
35	>2000	>2000
37	294	23
36	>2000	106
7-12	>2000	61
12-3	738	156
41	>2000	181
7-10	112	48
47	24.3	2.5
48	128.6	9
45	216	14
46	20	2
52	>2000	48
44	832	44
54	143	42
43	363	108
71	4	0.4
69-2	2.8	0.8
61	42.7	1.4
69	13.5	3
22-1	10.3	1.5
70	183	5.4
67	37	1.8
66	863.2	121

[1188] Conclusion: The parent thyromimetics tested had good to excellent affinity for the TR $\alpha$ 1 and/or TR $\beta$ 1 receptors. The prodrugs had poor affinity for the receptors and are therefore unlikely to exert a thyromimetic effect until activated in the liver.



Example B: Subacute Studies in Normal Mice/Rats Demonstrating Liver versus Heart Selectivity of Phosphonic Acid and Carboxylic Acid T3 Mimetics.

- [1189] The purpose of these studies was to compare the difference in efficacy, cardiac effects and endocrine effects between T3 and T3 mimetics that are carboxylic acids and T3 mimetics that are phosphonic acids. In one example, T3 and Compounds 7 and 17, which differ only in that for Compound 7 X is -P(O)OH<sub>2</sub> and for Compound 17 X is -C(O)OH, were compared. Efficacy endpoints include serum cholesterol, liver mitochondrial glycerol phosphate dehydrogenase (mGPDH) activity and the expression of relevant liver genes (e.g., the LDL-receptor, apoB, cpt-1, spot14 and apoA1). Safety parameters include heart weight, heart rate, heart mGPDH activity, the expression and key genes involved in cardiac structure and function (e.g., Serca2, HCN2, Kv1.5, MHC $\alpha$ , MHC $\beta$ , Alpha1c), and standard plasma chemistry analysis (liver enzymes, electrolytes, creatinine). Endocrine effects are monitored by analysis of serum thyroid stimulating hormone (TSH). [Taylor *et al.*, *Mol Pharmacol* 52(3): 542-7 (1997); Weitzel *et al.*, *Eur J Biochem* 268(14):4095-4103 (2001)]
- [1190] *Methods:* mGPDH activity was analyzed in isolated mitochondria using 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-phenyl tetrazolium chloride as the terminal electron acceptor (Gardner RS, *Analytical Biochemistry* 59:272 (1974)). Commercially available GPDH was used in each assay as a standard (Sigma, St. Louis, MO). Changes in levels of mRNA for liver and heart genes are analyzed using reverse transcriptase followed by real-time PCR analysis. The analysis is performed using an iCycler instrument (Biorad) and appropriate primers by means of standard methodology [e.g., Schwab DA *et al.* (2000) *Life Sciences* 66: 1683-94]. The amounts of mRNA are normalized to an internal control, typically, cyclophilin. Serum TSH is measured using an enzyme immunoassay (EIA) kit designed for rat TSH (Amersham Pharmacia Biotech, Arlington Heights, IL). Serum cholesterol is analyzed using a commercially available enzymatic kit (Sigma Diagnostics, St. Louis, MO).

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[1191] Normal rats (Sprague-Dawley) were maintained on a standard diet. Compounds 7 and 17, or T3 were administered by continuous infusion using an osmotic pump (Alzet; subcutaneous implant) at a dose of 1 mg/kg/day. The compounds were dissolved in 0.1N NaOH solution and the pH adjusted to 7.4-8.0. The compounds were brought up to an appropriate volume using PBS and BSA to maintain solubility within the pump. The compounds were chemically stable in the excipient at 37 °C for 7 days.

[1192] *Results:* Compound 7, a phosphonic acid T3 mimetic, produced a significant thyromimetic effect in the liver equivalent to that of T3 or Compound 17, a carboxylic acid T3 mimetic, without producing any significant effect in the heart. Compound 17 produced a significant thyromimetic effect comparable to that of T3 in both organs. Values are expressed as percent of control. (Table 4)

TABLE 4

	Liver GPDH	Heart GPDH	Heart Weight
control	100	100	100
T3	406	284	146
Compound 17	426	277	134
Compound 7	399	112	108

[1193] *Conclusion:* Based on mGPDH enzyme activity, Compound 7 had significant thyromimetic activity in the liver and none in the heart. In addition, Compound 7 did not cause cardiac hypertrophy. T3 and Compound 17, in contrast, did not show liver-selective thyromimetic effects. Thus, the results demonstrate that phosphonic acid T3 mimetics have a greater selectivity for the heart in terms of drug activity and distribution than carboxylic acid T3 mimetics.

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Example C: Subacute Studies in ZDF Rats Demonstrating  
Improved Therapeutic Index for Phosphonic Acid Containing T3  
Mimetics

[1194] ZDF rats were treated with either Compound 18 (a carboxylic acid T3 mimetic) or Compound *cis*-13-1 (a HepDirect prodrug of a phosphonic acid T3 mimetic) for 28 days dosed orally once a day. Compound 18 was administered at doses up to 5 mg/kg/d. Compound *cis*-13-1 was administered at doses up to 50 mg/kg/d. We reasoned that the ZDF rat, as a metabolically challenged animal model, would be more sensitive to the potential adverse cardiac effects of thyromimetics than a normal, cholesterol-fed rat. At sacrifice, heart rate, and the first derivative of left ventricular pressure (LV dP/dt) were measured with a Millar catheter inserted into the left ventricle. The therapeutic index (TI) for Compound 18 in the cholesterol-fed rat was 40 with respect to heart rate increases (Grover *et al.* PNAS 2003). The measurement of TI was a dose that ED15 for heart rate, *i.e.*, a dose that increased heart rate greater than or equal to 15% compared to the ED50 for cholesterol lowering. The therapeutic index for Compound 18 in the ZDF rats with respect to heart rate was 0.4, indicating that the model is much more sensitive to cardiac effects than a non-metabolically challenged animal. Additionally, the TI for LV dP/dt was 0.15. An increase in LV dP/dt of 25% was the value used in the TI calculation. The most sensitive measure of cardiac effects in this animal was LV dP/dt. ZDF rats treated with Compound *cis*-13-1 showed no changes in any of the parameters measured. Since we only dosed up to 50 mg/kg/d, we do not know the exact therapeutic index for some of these parameters. However, the TI improvement over Compound 18 is listed in the table below:

Parameter	TI Improvement
ED15 HR	>39
ED25 LV dP/dt	>102

- [1195] The reason that the TI is listed as greater than, *i.e.*, “>” is that the doses of Compound *cis*-13-1 were not high enough to reach the 15% or 25% threshold even at 50 mg/kg/d. By extrapolation with the cholesterol-fed rat for the Compound 18 data, the ZDF rats were 100-times more sensitive to the cardiac effects of the compound (a TI of ED15 HR/ED50 cholesterol from 40 in the normal rat to 0.4 in the ZDF rat). Therefore we calculate that the TI in a non-metabolically challenged animal would be >3900 with respect to heart rate and >10,000 with respect to LV dP/dt. We chose not to dose at such high levels at this time since the results from the ZDF animals demonstrated a significantly improved safety window. Thus the compounds of the present invention demonstrate a TI that is unexpected and vastly superior than carboxylic acid T3 mimetics.

#### Example D: Subacute Studies in Cholesterol-fed Rats

- [1196] The cholesterol-fed rat is an animal model of hypercholesterolemia generated by feeding the animals a diet with high cholesterol content. The purpose of these studies was to evaluate the effects of Compounds 7 and 17 on serum cholesterol (an efficacy parameter) and on heart weight and heart mGPDH activity (potential toxicity parameters).
- [1197] *Methods:* Rats were maintained on a diet containing 1.5% cholesterol and 0.5% cholic acid for 2 weeks prior to initiation of treatment. Serum cholesterol values were assessed and the animals randomized into groups for treatment. Serum cholesterol was analyzed using a commercially available enzymatic kit (Sigma Diagnostics, St. Louis, MO). Compound 17 and Compound 7 at various concentrations were administered IP once-a-day for seven days.
- [1198] *Results:* Doses of 0.1-1 mg/kg/day Compound 17 significantly decreased serum cholesterol. Doses of Compound 7 from 1-100 mg/kg/day significantly decreased serum cholesterol. The decreases of serum cholesterol at 1 mg/kg/day were identical for Compound 17 and Compound 7 (*see* Fig. 2). Undesirable cardiac hypertrophy was observed with Compound 17 at all doses

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which significantly decreased serum cholesterol, 0.1-1 mg/kg/day. No cardiac hypertrophy was observed with Compound 7 (*see* Fig. 3). Cardiac GPDH activity was also increased by Compound 17 at 1 mg/kg/day whereas a trend towards increased heart GPDH activity was observed with compound 7 only at 100 mg/kg (*see* Fig. 4). No adverse cardiac effects were observed with Compound 7 at any dose. These studies also indicate that cardiac weight is more sensitive to thyromimetic effects than GPDH activity.

- [1199] *Conclusion:* There is no separation between efficacy (cholesterol lowering) and toxicity (cardiac hypertrophy, induction of heart GPDH) for compound 17. Compound 7, in contrast, showed a therapeutic window of 10- to 100-fold. Thus, the results demonstrate that phosphonic acid T3 mimetics have a greater therapeutic window than carboxylic acid T3 mimetics.

#### Example E: Microsome/Primary Hepatocyte Stability Studies

##### i. Prodrug activation in Rat Liver Microsomes

- [1200] The purpose of these studies was to determine the kinetics of activation of prodrugs of thyromimetics in microsomal preparations. Microsomes contain the P450 enzyme that is required for the activation of many of the prodrugs prepared. The  $K_m$ ,  $V_{max}$ , and intrinsic clearance values determined are measures of prodrug affinity for the microsomal enzymes, the rate at which the prodrug is activated, and the catalytic efficiency with which the prodrug is activated, respectively.

- [1201] *Methods:* Activation of prodrugs by dexamethasone treated rat hepatocyte microsomes. Microsomes were isolated by standard differential centrifugation methods from dexamethasone-treated rats. The treatment is to increase cytochrome P450-3A (CYP3A4) activity. Induction of CYP3A4 was confirmed by an increase in testosterone hydroxylation.

- [1202] Various concentrations of HepDirect™ Compound 7 were incubated with rat hepatocytes microsomes. Compound 7 formation was analyzed by HPLC using UV-Vis detection. Kinetic parameters ( $V_{max}$  and  $K_m$ ) were

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calculated from the transformed data and the intrinsic clearance calculated from the kinetic parameters.

- [1203] *Results and conclusion:* Table 5 shows that prodrugs of Compound 7 are well activated in rat liver microsomes and have good affinity for the microsomal enzyme(s) catalyzing their activation:

TABLE 5

Compound	V <sub>max</sub> (pmol/min/mg)	K <sub>m</sub> (μM)	CL <sub>int</sub> (μL/min/mg)
13-1- <i>cis</i>	1746	31	56
13-6- <i>cis</i>	598	10	62
13-2- <i>cis</i>	694	8	86
13-3- <i>cis</i>	2118	46	46
13-5- <i>cis</i>	3266	113	29
Compound 12-3	775	14	54
13-4- <i>cis</i>	2983	100	30

ii. Activation of Prodrug by Human Liver S9

- [1204] Prodrugs are tested for conversion to their respective parent compounds by human liver S9. The S9 fraction is a fraction that contains both cytosolic and microsomal protein.
- [1205] *Method:* Reaction mixtures (0.5 mL at 37 °C) consist of 0.2 M potassium phosphate pH 7.4, 13 mM glucose-6-phosphate, 2.2 mM NADP<sup>+</sup>, 1 unit of glucose-6-phosphate dehydrogenase, 0-2.5 mg/mL human liver S9 fraction (In Vitro Technologies, Inc.), and up to 250 μM of prodrug. The activation of the prodrugs to the respective parent compounds is monitored by reverse phase HPLC or LC-MS/MS (Example F).
- [1206] *Results:* The rate of formation of the parent compound is measured. The enzyme kinetic parameters of V<sub>max</sub>, K<sub>m</sub> and intrinsic clearance CL<sub>int</sub> are calculated.
- [1207] *Conclusion:* Prodrugs of T3 mimetics are readily activated to their respective parent compound by human liver S9.

iii. Activation of Prodrug in Isolated Rat Hepatocytes

[1208] The purpose of these studies was to monitor the uptake and activation of the prodrugs of T3 mimetics to their respective active species in fresh, isolated rat hepatocytes.

[1209] Method: Hepatocytes are prepared from fed Sprague-Dawley rats (250-300 g) according to the procedure of Berry and Friend (Berry, M. N., Friend, D. S. J. *Cell Biol.* 43, 506-520 (1969)) as modified by Groen (Groen, A. K. *et al.*, *Eur J. Biochem* 122, 87-93 (1982)). Hepatocytes (60 mg wet weight/ mL) are incubated in 1 mL Krebs-bicarbonate buffer containing 10 mM glucose, and 1 mg/ mL BSA. Incubations are carried out in a 95% oxygen, 5% carbon dioxide atmosphere in closed, 50-mL Falcon tubes submerged in a rapidly shaking water bath (37 °C). Prodrugs are dissolved in DMSO to yield 10 mM stock solutions, and then diluted into the cell suspension to yield a final concentration of 100 µM. At appropriate time points over the course of 1 h, aliquots of the cell suspension are removed and spun through a silicon/mineral oil layer into 10% perchloric acid. The cell extracts in the acid layers are neutralized, and the intracellular prodrug metabolite content analyzed by reverse phase HPLC or LC-MS/MS (Example F). The AUC of the active species in the hepatocytes is calculated from the concentration-time profile of parent compound.

[1210] Results: Results are shown in Table 6 below:

TABLE 6

Compound	AUC (0-2h) (nmole*h/g)
Compound 13-1- <i>cis</i>	967
Compound 13-6- <i>cis</i>	433
Compound 13-2- <i>cis</i>	533
Compound 3-3- <i>cis</i>	459
Compound 13-5- <i>cis</i>	1988
Compound-13-7- <i>cis</i>	806
Compound 13-4- <i>cis</i>	784

[1211] *Conclusion:* Prodrugs of T3 mimetics are readily taken up and activated to their active species in fresh rat hepatocytes.

### Example F: Oral Bioavailability/Efficacy Studies in Normal Rats

#### i. Oral Bioavailability

[1212] The oral bioavailability (OBAV) of Compound 12-1, a bisPOM prodrug of Compound 7, was estimated by comparison of the dose-normalized area under the curve (AUC) of the plasma concentration-time profile of Compound 7 following IV and PO administration of Compound 7 and Compound 12-1, respectively, to normal rats.

[1213] *Method:* Groups of non-fasted male SD rats were administered either 5 mg/kg of Compound 7 by IV bolus or 20 mg/kg of Compound 12-1 by oral gavage. Prior to drug administration, the rats were catheterized at the tail artery to facilitate blood collection. Plasma samples were obtained at pre-specified time points following dosing, extracted with 1.5 volumes of methanol, and then assayed by an LC-UV method using a C18 column eluted with a gradient of 20% to 45% v/v acetonitrile in a potassium phosphate buffer pH 6.2 over 15 min with UV absorbance monitoring at 280 nm. The AUC values were determined noncompartmentally from the plasma concentration-time plots by trapezoidal summation to the last measurable time point.

[1214] In another experiment the OBAV of Compound 19-2, a phosphonic acid T3 mimetic, was assessed using catheterized rats. Plasma levels of compound were analyzed by HPLC and the AUCs for the i.v. dose of 5 mg/kg and the p.o. dose of 20 mg/kg were compared. The maximum OBAV for Compound 19-2 was 0.003%. Typically, compounds that are taken forward as an oral drug candidate have OBAV values of at least 15-20%, when tested in an animal model. This minimal requirement for OBAV in a genetically homogenous model system insures that exposure can be accurately monitored when humans are treated with the compound. Furthermore, in a genetically variable background such as humans, the variability for a compound with low OBAV in genetically homogenous model systems, can be widely variable, leading some subjects to have much higher than anticipated exposure, while other subjects have no exposure. OBAV of Compound *cis*-13-1 is calculated



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to be 25% when AUC's of Compound cis-13-1 are used and to be 40-50% when comparing the AUC's of Compound 7 using serial plasma samples of a i.v. administered compound versus a p.o. administered compound. The liver levels at 1.5h post-dosing of Compound 7 and prodrugs thereof are listed in Table 7, example F (ii).

- [1215] *Results:* Compound 12-1 was adequately absorbed in the rat with an estimated OBAV of 25%. Following oral administration of the prodrug, the plasma concentrations of the generated Compound 7 ( $C_{max} = 1.2 \pm 0.2 \mu\text{g/mL}$  at a  $T_{max} = 3 \pm 1 \text{ hr}$ ) were sustained over an 8 h period ( $t_{1/2} = 6 \pm 6 \text{ hr}$ ). Compound 19-2 was not adequately absorbed.

- [1216] *Conclusion:* Adequate systemic exposure of Compound 7 was maintained over 8 h after an oral administration of Compound 12-1 to rats.

ii. Liver Distribution Following Oral Administration

- [1217] Liver levels of Compound 7 were assessed in normal rats following oral administration of the HepDirect™ or other prodrugs. The levels were used to estimate potential efficacy. Liver levels were assessed by LC-MS using the 363.3/63.0 peak area to estimate levels of Compound 7 generated by orally administered prodrugs.

- [1218] *Results:* Results are shown in Table 7.

TABLE 7

Compound	Liver Levels (ug/g) (10 mg/kg@1.5h)
Compound 7	Not Detected
Compound 12-1	1.39
Compound 13-1- <i>cis</i>	0.98
Compound 13-6- <i>cis</i>	0.39
Compound 13-2- <i>cis</i>	0.25
Compound 13-3- <i>cis</i>	0.77
Compound 12-2	0.67
Compound 13-5- <i>cis</i>	0.56
Compound 13-7- <i>cis</i>	0.23
Compound 13-4- <i>cis</i>	0.32

- [1219] *Conclusion:* All compounds tested produced adequate liver levels of compound 7. All are predicted to induce thyromimetic effects *in vivo* following oral administration.

### Example G: Oxygen Consumption Study

- [1220] Thermogenesis is a measurement of energy consumption. Compounds that increase thermogenesis are likely to increase caloric expenditure and thereby cause body weight loss and its associated benefits to metabolic status (*e.g.*, insulin sensitivity). Thermogenesis is assessed in subcellular fractions of various tissues, isolated cells, whole tissues, or in whole animals using changes in oxygen consumption as the endpoint. Oxygen is used up when calories are burned by various metabolic processes.
- [1221] *Methods:* Animals are dosed once or several times a day via a parenteral or oral route for a treatment period ranging from 1 day to several weeks. Oxygen consumption is measured following a single or multiple days of treatment.
- [1222] Mitochondrial thermogenesis is measured polarographically with a Clark-type oxygen electrode using mitochondria isolated from various tissues, including liver. Mitochondria are isolated by differential centrifugation. As those skilled in the art are familiar, state 3 respiration or cytochrome c oxidase activity are measured in isolated mitochondria. The mitochondria are incubated at 30 °C in a buffered medium containing 80 mM KCl, 50 mM HEPES, 5 mM KH<sub>2</sub>PO<sub>4</sub>, 1 mM EGTA, 0.1% (w/v) fatty acid-free bovine serum albumin (BSA), pH 7.0 in the presence of 10 mM succinate, 3/75  $\mu$ M rotenone and 0.3 mM ADP (Iossa, S, *FEBS Letters*, 544: 133-7 (2003)).
- [1223] Oxygen consumption rates are measured in isolated hepatocytes using a portable Clark-type oxygen electrode placed in the hepatocyte medium. Hepatocytes are isolated from liver using a two-step collagenase perfusion (Berry, M. N., Friend, D. S. *J. Cell Biol.* 43: 506-520 (1969)) as modified by Groen (Groen, A. K. *et al.*, *Eur J. Biochem* 122: 87-93 (1982)). Non-

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parenchymal cells are removed using a Percoll gradient and the cells are resuspended in tissue culture medium in a spinner flask. The oxygen consumption of the cells is measured over time once the system is sealed.

[1224] Oxygen consumption is measured in isolated perfused liver (Fernandez, V., *Toxicol Lett.* 69:205-10(1993)). Liver is perfused *in situ* and oxygen consumption is calculated by measuring the difference between the oxygen saturation of the inflow buffer and the outflow buffer maintained at a constant flow.

[1225] In one assay, whole animal oxygen consumption is measured using an indirect calorimeter (Oxymax, Columbus Instruments, Columbus, OH). Animals are removed from their cages and placed in the chambers. The resting oxygen consumption is measured in animals during periods of inactivity as measured by activity monitors. The oxygen consumption is calculated based on the flow through the chamber and the difference in oxygen partial pressures at the inflow and outlet ports. Carbon dioxide (CO<sub>2</sub>) efflux is also measured in parallel using a CO<sub>2</sub> electrode.

[1226] Male Sprague Dawley rats were treated with 3, 10, or 30 mg/kg/d of Compound cis-13-1 orally for 14 days. Rats were placed in the FoxBox apparatus (Sable Systems, Las Vegas, NV), allowed to acclimate and the resting oxygen consumption was measured. The oxygen consumption rates were compared to pre-dose measurements taken on each individual animal. Oxygen consumption following treatment was 116, 125, 132% of the pre-dose rate, for 3, 10, and 30, respectively. Thus, the compounds of the present invention are useful in increasing oxygen consumption.

#### Example H: Tissue Distribution Studies

[1227] The tissue distribution and the pharmacokinetics of Compound 7 and the Compound 17 were assessed following IP administration to normal rats.

[1228] *Method:* In separate studies, the T3 mimetic phosphonate Compound 7 and its carboxylate analog Compound 17 were administered at 10 mg/kg to groups of male SD rats via the peritoneal cavity. At pre-selected time points

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following dosing, the rats were anesthetized using iso-fluorane and the peritoneal cavity was then opened and a blood sample was obtained from the abdominal vena cava. In addition, liver, kidney, and heart were excised and immersed in 3 volumes of cold 60% acetonitrile. The blood samples were briefly centrifuged and the plasma fraction was then extracted with 1.5 volumes of methanol, processed, and analyzed by LC-UV as described in Example G. The frozen liver, kidney, and heart tissue were homogenized in 60% v/v acetonitrile, centrifuged, and then analyzed by LC-UV. Pharmacokinetic parameters and AUC of the plasma and tissue concentration-time profiles were determined noncompartmentally by WinNonLin.

- [1229] *Results:* The following plasma pharmacokinetics were calculated for Compound 17 and Compound 7 and shown in Table 8.

TABLE 8

PARAMETER	UNIT	Compound 17	Compound 7
Dosing time	hr	0	0
Rsq		0.9966	0.9893
Tmax	hr	0.3333	0.3333
Cmax	µg/mL	3.49	25.97
Tlast	hr	2	4
Vz(observed)/F	L/kg	2.2049	0.4008
Cl(observed)/F	L/hr/kg	3.3628	0.3006
AUMClast	µg*hr <sup>2</sup> /mL	1.7683	33.7098

- [1230] The AUC values of the plasma and tissue concentration-time profiles were calculated for Compound 17 and Compound 7 and shown in Table 9.

TABLE 9

T3 Mimetic	Plasma AUC	Liver AUC	Heart AUC	Kidney AUC
Compound 17	2.8 µg-hr/mL	48.5 nmol-hr/g	27.6 nmol-hr/g	1.1 nmol-hr/g
Compound 7	31.6 µg-hr/mL	301.7 nmol-hr/g	32.8 nmol-hr/g	5.0 nmol-hr/g

- [1231] *Conclusion:* Compared to the phosphonic acid T3 mimetic (Compound 7), the carboxylic acid T3 mimetic (Compound 17) had significantly higher plasma clearance and volume of distribution in the rat. Substantially higher levels of Compound 7 measured in the liver indicated good penetration of the T3 mimetic phosphonate into the target organ. Compound 7 showed higher liver exposure relative to Compound 17. Thus, phosphonic acid T3 mimetics have greater liver specificity, as compared to heart tissue, than do carboxylic acid T3 mimetics.

#### Example I: Subacute Studies in Cholesterol fed Rats Cholesterol Reduction

- [1232] The purpose of these studies was to evaluate the effects of a carboxylic acid T3 mimetic (Compound 18) a phosphonic acid T3 mimetic prodrug (Compound 13-1-cis) on serum cholesterol and TSH levels, hepatic and cardiac gene expression and enzyme activities, heart weight, and clinical chemistry parameters.
- [1233] *Methods:* Rats were maintained on a diet containing 1.5% cholesterol and 0.5% cholic acid for 2 weeks prior to initiation of treatment. Serum cholesterol values were assessed and the animals randomized into groups for treatment. Serum cholesterol was analyzed using a commercially available enzymatic kit (Sigma Diagnostics, St. Louis, MO). Compound 13-1-cis and Compound 18 were administered PO once a day for seven days. Serum TSH is measured using an enzyme immunoassay (EIA) kit designed for rat TSH (Amersham Pharmacia Biotech, Arlington Heights, IL). Expression levels of liver genes (e.g., the LDL-receptor, apoB, cpt-1, spot14 and apoA1) and heart genes (e.g., Serca2, HCN2, Kv1.5, MHC $\alpha$ , MHC $\beta$ , Alpha1c) are quantified by Northern blot analysis or by RT-PCR. For Northern analyses, RNA is isolated from liver tissue by a guanidinium thiocyanate method, and total RNA is obtained using an RNeasy column (Qiagen). mRNA is separated on a 1% agarose gel and transferred to a nylon membrane. Oligonucleotides specific for the complementary gene sequences are used to make <sup>32</sup>P-labeled probes (Multiprime DNA labeling systems, Amersham Pharmacia Biotech).

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Following hybridization of the probes to the nylon membranes, radioactivity is assessed on a blue film (Eastman Kodak Co.), and the resulting image quantified using the appropriate software. RT-PCR is performed using an iCycler instrument (Biorad) using appropriate primers by means of standard methodology [e.g., Schwab DA *et al.* (2000) *Life Sciences* 66: 1683-94]. GPDH activity in liver and heart are measured as described in Example B. The activities of PEPCK and glucose 6-phosphatase in liver are measured by means of direct enzymatic assays of homogenized liver tissue as described by Andrikopoulos S *et al.* (1993) *Diabetes* 42: 1731-1736. Alternatively, expression levels of the corresponding genes are determined by Northern blot analysis or RT-PCR as described above.

[1234] *Results:* Doses of 0.6-50 mg/kg/day of Compound 13-1-*cis* significantly decreased serum cholesterol (see Figure 5). Compound 18 at 1 mg/kg/day significantly decreased serum cholesterol. No significant undesirable cardiac hypertrophy was observed with Compound 13-1-*cis* at any dose tested.

[1235] *Conclusion:* Compound 13-1 showed significant cholesterol lowering even at the lowest dose evaluated (0.6 mg/kg). Furthermore, no evidence of undesirable effects on heart weight was observed across the entire dose range tested (up to 50 mg/kg).

#### Example J: Decreases In Hepatic Fat Content Following Treatment With A Phosphonic Acid Thyromimetic:

[1236] Normal rats were chronically infused with Compound 7 for 7 days. Liver triglycerides were analyzed following lipid extraction by the Bligh Dyer method (Bligh EG and Dyer WJ, A rapid method of total lipid extraction and purification. *Can J Med Sci.* 1959 (August); 37(8):911-7, incorporated herein by reference). Total triglycerides were analyzed in the liver extracts by an enzymatic assay (Thermo Electron Corporation). Total lipid was normalized to initial liver weight and triglyceride content was normalized to liver weight. T3 administration would not be expected to decrease liver triglyceride content. Analysis of hepatic triglyceride content in the T3 infused rats showed no

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significant decrease in triglyceride content. There was a 4% reduction in liver triglycerides for this group and the results were not statistically significant. The Compound 7 infused animals demonstrated a decrease in hepatic triglyceride content of 64%, an unexpected and significantly different result.

- [1237] In other experiments, Compound 7 was orally administered to ZDF rats for 28 days. Liver triglycerides were analyzed as described above. Total liver triglycerides were reduced in the treated animals 42% in the 2.5 mg/kg/d group. Histologic analysis of liver sections following H&E staining demonstrated a pronounced and diffuse microvesicular steatosis throughout the hepatic lobule in the vehicle treated group. The hepatic steatosis is a well known and described phenomenon for the ZDF rat, and therefore not attributable to vehicle treatment. There was a dose dependent reduction in the microvesicular steatosis and a noticeable appearance of intact cytoplasm within the hepatocytes consistent with a non-steatotic liver.

#### Example K: Effects of Phosphonic Acid T3 Mimetic Prodrugs *In Vivo* on Cholesterol

- [1238] Another experimental assay was to evaluate the effects of prodrugs of phosphonic acid T3 mimetics of the present invention on serum cholesterol. Rats were made hypercholesterolemic by maintenance on a diet containing 1.5% cholesterol and 0.5% cholic acid for at least 2 weeks prior to initiation of treatment. Plasma cholesterol values were assessed prior to and following treatment and the effects of compound were expressed as a percentage change from the pre-dose cholesterol levels. Total cholesterol was analyzed using a commercially available enzymatic kit (Sigma Diagnostics, St. Louis, MO). Compounds were routinely tested for oral efficacy at a dose of 0.5 mg/kg/d. Hypercholesterolemic rats were treated with vehicle, Compound 13-1-*cis* (a HepDirect version of Compound 7), Compound 19-1 (a diethyl ester of Compound 19-2), Compound 13-9 (a HepDirect version of Compound 19-2), Compound 12-5 (a bisPom version of compound 19-2), or Compound 15-5 (a bisamidate version of Compound 19-2) at 0.5 mg/kg/d orally. Compound 13-1-*cis* has been extensively characterized and was used as the positive control

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for the assay. Vehicle, Compound 13-9 and Compound 19-1 failed to demonstrate cholesterol lowering in this assay while Compound 13-1-*cis*, Compound 12-5 and Compound 15-5 demonstrated a significant lowering of cholesterol. HepDirect versions of the phosphonic acid T3 mimetics normally show good results, however, diethyl ester versions of the phosphonic acid T3 mimetics of the present invention were found not to be suitable as prodrugs.

[1239] In another experiment, the efficacy of Compound 7 was compared to Compounds 12-9, *cis*-13-2 and 15-6, which are prodrugs of a compound that binds poorly to both TR $\alpha$  and TR $\beta$  (K<sub>i</sub> of about 300nM). Compound 7 was efficacious whereas Compounds 12-9, *cis*-13-2 and 15-6 were not efficacious in lowering cholesterol.

[1240] Table 10 (below) shows the results for additional compounds of the present invention assayed in the present method.

**TABLE 10**

<u>Compound delivered i.p</u> <u>(0.2 mg/kg/d)</u>	<u>% Cholesterol</u> <u>Lowering</u>
Untreated	-3.6
Vehicle	-5.3
40	-64.2
7-5	-63.3
7-9	-63.2
24-3	-48.6
8-2	-48.0
45	-46.3
7-3	-45.4
22	-44.0
66	-42.9
7	-41.5
11	-36.4



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24-1	-35.4
7-14	-32.9
33	-32.5
46	-29.6
47	-29.3
42	-28.8
7-8	-28.6
7-10	-25.8
8	-24.3
48	-23.4
29	-21.9
38	-21.7
31	-21.1
27	-20.8
24-2	-20.5
28	-20.5
6	-20.5
19	-19
52	-18.8
7-6	-13.5
37	-0.4

<u>Compound delivered p.o.</u> <u>(0.5 mg/kg/d)</u>	<u>% Cholesterol</u> <u>Lowering</u>
Untreated	-4.0
Vehicle	-5.1
15-4	-39.6
12-8	-33.7
12-5	-32.5
<i>cis</i> -13-1	-31.8
12-4	-30.5
15-5	-29.9

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15-7	-29.1
13-8	-26.5
13-11	-24.8
13-9	-10.9
19-1	-6.6
12-7	-39.1
13-10	-25.8
15-8	-31.1

<u>Compound delivered p.o.</u>	<u>% Cholesterol</u>
<u>(0.2 mg/kg/d)</u>	<u>Lowering</u>
Vehicle	-5.1
71	-54.4
69-2	-49.9
69	-41.9
45	-40.4
7-9	-38.4
7-5	-38.0
7-3	-36.5
61	-33.7
70	-32.8
8-1	-32.2
40	-27.3
46	-23.8
8	-20.6
22-1	-19.9
67	-17.0
22	-16.5
66	-12.5
7-1	-12.2
11	-5.1

Example L: Effects of Phosphonic Acid T3 Mimetic Prodrugs *In Vivo* on Circulating TSH

[1241] Another concern with synthetic thyromimetics is the suppression of the endogenous thyroid axis. Thyroid homeostasis is maintained by the action of thyroid releasing hormone (TRH) and thyroid stimulating hormone (TSH). TRH is produced in the paraventricular region of the hypothalamus (Dupre, SM et al, Endocrinology 145:2337-2345 (2004)). TRH acts on the pituitary releasing TSH which then acts on the thyroid organ itself. The levels of TRH and TSH are controlled by a feed-back sensing mechanism so that low levels of thyroid hormone (TH) (T3 or T4) will cause an increase in TRH and TSH and elevated levels of TH will cause a suppression of TRH and TSH. Because TSH can be measured more readily than TRH, levels of TSH are tested as a measure of systemic effects of TH or synthetic thyromimetics. Decreased TSH levels are a concern because suppression of the thyroid axis could lead to systemic hypothyroidism. Although this particular side effect has been noted, it has typically been treated with less concern than the cardiac safety issues. However, new evidence indicates that, in addition to possible systemic hypothyroidism, which is a concern for any potential long-term therapy, TSH suppression will enhance osteoclast function leading to a decrease in bone mass and loss of bone structural integrity (Abe, E et al, Cell 115:151-62 (2003)). Therefore previous investigators have measured TSH levels when testing synthetic thyromimetics and have used a 30% decrease of TSH as the denominator in their therapeutic index calculations. The therapeutic index of TSH levels in cholesterol-fed rats, treated with either Compound 17 or Compound 18 (both carboxylic acid T3 mimetics) for 7 days, are 0.8 and 0.4, respectively. Therefore, both compounds suppress TSH as doses lower than that required to decrease circulating cholesterol. In ZDF rats treated with 50 mg/kg/d Compound 7 for 28 days, no statistically significant difference from vehicle was measured for TSH. However, 0.2 mg/kg/d of Compound 18 in 28 day treated ZDF rats, decreased TSH levels greater than 90%. In mice treated with 10 mg/kg/d Compound 7 for 77 days, no decrease in TSH was observed,

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indicating that Compound 7 can significantly decrease cholesterol levels without producing an adverse effect on the endogenous thyroid axis.

#### Example M: Effects of Phosphonic Acid T3 Mimetic Prodrugs In Vivo on Glucose

- [1242] Plasma glucose in Compound 7 treated ZDF rats at sacrifice decreased from 618 mg/dL to 437 mg/dL following 4 weeks of treatment with Compound *cis*-13-1. The decrease was dose dependent. Blood glucose levels at those doses corresponded to 442 mg/dL and 243 mg/dL, respectively. Similar changes were also evident at two weeks, post-treatment. There was a dose-dependent decrease in the water consumption of the treated animals, which is consistent with an improvement in glycemic control.

#### Example N: T3 and T3 mimetic mediated myosin heavy chain gene transcription in the heart

- [1243] An RT-PCR assay as disclosed in: Sara Danzi, Kaie Ojamaa, and Irwin Klein *Am J Physiol Heart Circ Physiol* 284: H2255-H2262, 2003 (incorporated herein by reference) is used to study both the time course and the mechanism for the triiodothyronine (T3)-induced transcription of the  $\alpha$ - and  $\beta$ -myosin heavy chain (MHC) genes in vivo on the basis of the quantity of specific heterogeneous nuclear RNA (hnRNA). The temporal relationship of changes in transcriptional activity to the amount of  $\alpha$ -MHC mRNA and the coordinated regulation of transcription of more than one gene in response to T3 and T3 mimetics are demonstrated. Analysis of a time course of T3 and T3 mimetics that are not liver specific show mediated induction of  $\alpha$ -MHC hnRNA and repression of  $\beta$ -MHC hnRNA, whereas no significant affect is observed with compounds of the present invention at doses that are therapeutically useful.

### Example O: Cardiovascular activity of T3 Mimetics in the Rat

- [1244] The objective of these experiments was to evaluate the effect of phosphonic acid containing T3 mimetics versus carboxylic acid containing T3 mimetics, on cardiovascular function (heart rate, inotropic state, and aortic pressure) in the Sprague Dawley (SD) rat model.
- [1245] *Method:* Compound *cis*-13-1 (a HepDirect prodrug of Compound 7) was dissolved in PEG400 and administered daily to SD male rats (n=6/group) by oral gavage (1, 5, 10, 30, 50 mg/kg/day) at 1 ml/kg body weight. The control group (n=6) was given vehicle only. Compound 18 (a carboxylic acid T3 mimetic) was administered at 1 mg/kg p.o. as a positive control (n=6). On the 7th day after the start of dosing, animals were anesthetized with Isoflurane and the left ventricle cannulated with a high fidelity catheter tip transducer via the right carotid artery. Left ventricular pressure, its first derivative (LVdP/dt), lead I ECG, and heart rate (HR) triggered off the ECG waveform, were digitally recorded. LV dP/dt is a well accepted measure of inotropic state. Systolic and diastolic aortic pressures were measured by retracting the catheter into the proximal aorta.
- [1246] *Results:* Compared to vehicle treated animals, Compound 18 administration resulted in marked and statistically significant increases in HR, LV dP/dt, and systolic aortic pressure after 7 days of treatment. In contrast, HR, LV dP/dt, systolic and diastolic aortic pressures in all groups treated with Compound *cis*-13-1 were not significantly different compared to vehicle treated animals. Heart weight and heart weight normalized to body weight in Compound 18 treated animals were significantly increased compared to control animals. There were no significant changes in heart weight or heart weight/body weight ratios in Compound *cis*-13-1 treated groups.
- [1247] *Conclusions:* It is concluded that Compound *cis*-13-1 when administered at doses up to 50 mg/kg/day for 7 days is devoid of significant chronotropic and inotropic effects in the normal SD rat. This stands in contrast to Compound 18 which is associated with marked effects when given at 1 mg/kg/day.

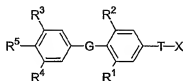
## Example P: Continuous Infusion Study

- [1248] Screening for thyromimetic activity was performed in normal rats maintained on a cholesterol-containing diet. Compounds were administered by continuous infusion using an osmotic pump at 1 mg/kg/day. The compounds were dissolved in 0.1N NaOH solution and the pH adjusted to 7.4-8.0. The compounds were chemically stable as an aqueous solution at 37°C for 14 days.
- [1249] Compounds 7, 69, 70, and 69-1 were compared to 17 and vehicle testing changes in heart rate, LV dP/dt, systolic and diastolic blood pressure, and reductions in total cholesterol. Compound 17 increased heart rate by 40% when analyzed at day 7 and the elevation was through d14. At the end-of-life it was demonstrated that Compound 17 also increased LV dP/dt by 71% and left ventricular weight. Systolic and diastolic blood pressure was also increased by 30%. Compound 17 produced a significant decrease in cholesterol when measured at day 7, but no significant decrease in cholesterol was observed at day 14. For some reason, Compound 17 ceased to produce a cholesterol-lowering effect at the longer time, while still maintaining adverse cardiovascular effects.
- [1250] Compounds 7, 69, 70, and 69-1 demonstrated no changes in any of the cardiovascular parameters at either day 7 or day 14. Compounds 7, 69, 70, and 69-1 demonstrated cholesterol lowering effects at day 7 and at day 14. Reductions in cholesterol at day 7 were equivalent for all the compounds tested.
- [1251] Having now fully described the invention, it will be understood by those of skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the invention or any embodiment thereof. All patents, patent applications and publications cited herein are fully incorporated by reference herein in their entirety.

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What is Claimed Is:

1. A compound of Formula I:



wherein:

G is selected from the group consisting of -O-, -S-, -Se-, -S(=O)-, -S(=O)<sub>2</sub>-, -CH<sub>2</sub>-, -CF<sub>2</sub>-, -CHF-, -C(O)-, -CH(OH)-, -NH-, and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)-, or CH<sub>2</sub> linked to any of the preceding groups;

or G is R<sup>50</sup>-R<sup>51</sup> wherein;

R<sup>50</sup>-R<sup>51</sup> together are -C(R<sup>52</sup>)=C(R<sup>52</sup>)- or alternatively R<sup>50</sup> and R<sup>51</sup> are independently selected from O, S and -CH(R<sup>53</sup>)-, with the provisos that at least one R<sup>50</sup> and R<sup>51</sup> is -CH(R<sup>53</sup>)-, and when one of R<sup>50</sup> and R<sup>51</sup> is O or S, then R<sup>53</sup> is R<sup>54</sup>;

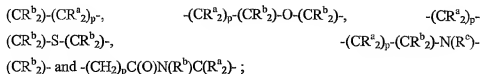
R<sup>54</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

R<sup>53</sup> is selected from hydrogen, halogen, hydroxyl, mercapto, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

R<sup>52</sup> is selected from hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

T is selected from the group consisting of -(CR<sup>a</sup>)<sub>k</sub>-, -CR<sup>b</sup>=CR<sup>b</sup>-(CR<sup>a</sup>)<sub>n</sub>-, -(CR<sup>a</sup>)<sub>n</sub>-CR<sup>b</sup>=CR<sup>b</sup>-, -(CR<sup>a</sup>)<sub>2</sub>-CR<sup>b</sup>=CR<sup>b</sup>-(CR<sup>a</sup>)<sub>2</sub>-, -O(CR<sup>b</sup>)<sub>2</sub>(CR<sup>a</sup>)<sub>n</sub>-, -S(CR<sup>b</sup>)<sub>2</sub>(CR<sup>a</sup>)<sub>n</sub>-, -N(R<sup>c</sup>)(CR<sup>b</sup>)<sub>2</sub>(CR<sup>a</sup>)<sub>n</sub>-, -N(R<sup>b</sup>)C(O)(CR<sup>a</sup>)<sub>n</sub>-, -(CR<sup>a</sup>)<sub>m</sub>C(R<sup>b</sup>)(NR<sup>b</sup>R<sup>c</sup>)-, -C(O)(CR<sup>a</sup>)<sub>m</sub>-, -(CR<sup>a</sup>)<sub>m</sub>C(O)-, -(CR<sup>b</sup>)<sub>2</sub>-O-(CR<sup>b</sup>)<sub>2</sub>-(CR<sup>a</sup>)<sub>p</sub>-, -(CR<sup>b</sup>)<sub>2</sub>-S-(CR<sup>b</sup>)<sub>2</sub>-(CR<sup>a</sup>)<sub>p</sub>-, -(CR<sup>b</sup>)<sub>2</sub>-N(R<sup>c</sup>)-

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k is an integer from 0-4;

m is an integer from 0-3;

n is an integer from 0-2;

p is an integer from 0-1;

Each  $\text{R}^a$  is independently selected from the group consisting of hydrogen, optionally substituted  $-\text{C}_1\text{-C}_4$  alkyl, halogen,  $-\text{OH}$ , optionally substituted  $-\text{O}-\text{C}_1\text{-C}_4$  alkyl,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{F}$ , optionally substituted  $-\text{S}-\text{C}_1\text{-C}_4$  alkyl,  $-\text{NR}^b\text{R}^c$ , optionally substituted  $-\text{C}_2\text{-C}_4$  alkenyl, and optionally substituted  $-\text{C}_2\text{-C}_4$  alkynyl; with the proviso that when one  $\text{R}^a$  is attached to C through an O, S, or N atom, then the other  $\text{R}^a$  attached to the same C is a hydrogen, or attached via a carbon atom;

Each  $\text{R}^b$  is independently selected from the group consisting of hydrogen and optionally substituted  $-\text{C}_1\text{-C}_4$  alkyl;

Each  $\text{R}^c$  is independently selected from the group consisting of hydrogen, optionally substituted  $-\text{C}_1\text{-C}_4$  alkyl, optionally substituted  $-\text{C}(\text{O})-\text{C}_1\text{-C}_4$  alkyl, and  $-\text{C}(\text{O})\text{H}$ ;

$\text{R}^1$  and  $\text{R}^2$  are each independently selected from the group consisting of halogen, optionally substituted  $-\text{C}_1\text{-C}_4$  alkyl, optionally substituted  $-\text{S}-\text{C}_1\text{-C}_3$  alkyl, optionally substituted  $-\text{C}_2\text{-C}_4$  alkenyl, optionally substituted  $-\text{C}_2\text{-C}_4$  alkynyl,  $-\text{CF}_3$ ,  $-\text{CHF}_2$ ,  $-\text{CH}_2\text{F}$ ,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{F}$ , optionally substituted  $-\text{O}-\text{C}_1\text{-C}_3$  alkyl, and cyano;

$\text{R}^3$  and  $\text{R}^4$  are each independently selected from the group consisting of hydrogen, halogen,  $-\text{CF}_3$ ,  $-\text{CHF}_2$ ,  $-\text{CH}_2\text{F}$ ,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{F}$ , cyano, optionally substituted  $-\text{C}_1\text{-C}_{12}$  alkyl, optionally substituted  $-\text{C}_2\text{-C}_{12}$  alkenyl, optionally substituted  $-\text{C}_2\text{-C}_{12}$  alkynyl, optionally substituted  $-(\text{CR}^a_2)_m\text{aryl}$ , optionally substituted  $-(\text{CR}^a_2)_m\text{cycloalkyl}$ , optionally substituted  $(\text{CR}^a_2)_m\text{heterocycloalkyl}$ ,  $-\text{C}(\text{R}^b)=\text{C}(\text{R}^b)\text{-aryl}$ ,  $-\text{C}(\text{R}^b)=\text{C}(\text{R}^b)\text{-cycloalkyl}$ ,  $-\text{C}(\text{R}^b)=\text{C}(\text{R}^b)\text{-heterocycloalkyl}$ ,  $-\text{C}\equiv\text{C}(\text{aryl})$ ,  $-\text{C}\equiv\text{C}(\text{cycloalkyl})$ ,  $-\text{C}\equiv\text{C}(\text{heterocycloalkyl})$ ,  $-(\text{CR}^a_2)_n(\text{CR}^b_2)\text{NR}^f\text{R}^g$ ,  $-\text{OR}^d$ ,  $-\text{SR}^d$ ,



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-S(=O)R<sup>e</sup>, -S(=O)<sub>2</sub>R<sup>e</sup>, -S(=O)<sub>2</sub>NR<sup>f</sup>R<sup>g</sup>, -C(O)NR<sup>f</sup>R<sup>g</sup>, -C(O)OR<sup>h</sup>, -C(O)R<sup>e</sup>, -N(R<sup>b</sup>)C(O)R<sup>e</sup>, -N(R<sup>b</sup>)C(O)NR<sup>f</sup>R<sup>g</sup>, -N(R<sup>b</sup>)S(=O)<sub>2</sub>R<sup>e</sup>, -N(R<sup>b</sup>)S(=O)<sub>2</sub>NR<sup>f</sup>R<sup>g</sup>, and -NR<sup>f</sup>R<sup>g</sup>;

Each R<sup>d</sup> is selected from the group consisting of optionally substituted -C<sub>1</sub>-C<sub>12</sub> alkyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkenyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkynyl, optionally substituted -(CR<sup>b</sup>)<sub>n</sub>aryl, optionally substituted -(CR<sup>b</sup>)<sub>n</sub>cycloalkyl, optionally substituted -(CR<sup>b</sup>)<sub>n</sub>heterocycloalkyl, and -C(O)NR<sup>f</sup>R<sup>g</sup>;

Each R<sup>e</sup> is optionally substituted -C<sub>1</sub>-C<sub>12</sub> alkyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkenyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkynyl, optionally substituted -(CR<sup>a</sup>)<sub>n</sub>aryl, optionally substituted -(CR<sup>a</sup>)<sub>n</sub>cycloalkyl, and optionally substituted -(CR<sup>a</sup>)<sub>n</sub>heterocycloalkyl;

R<sup>f</sup> and R<sup>g</sup> are each independently selected from the group consisting of hydrogen, optionally substituted -C<sub>1</sub>-C<sub>12</sub> alkyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkenyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkynyl, optionally substituted -(CR<sup>b</sup>)<sub>n</sub>aryl, optionally substituted -(CR<sup>b</sup>)<sub>n</sub>cycloalkyl, and optionally substituted -(CR<sup>b</sup>)<sub>n</sub>heterocycloalkyl, or R<sup>f</sup> and R<sup>g</sup> may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4 unsaturations, which may contain a second heterogroup selected from the group of O, NR<sup>e</sup>, and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally substituted -C<sub>1</sub>-C<sub>4</sub> alkyl, -OR<sup>b</sup>, oxo, cyano, -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, optionally substituted phenyl, and -C(O)OR<sup>h</sup>;

Each R<sup>h</sup> is selected from the group consisting of optionally substituted -C<sub>1</sub>-C<sub>12</sub> alkyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkenyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkynyl, optionally substituted -(CR<sup>b</sup>)<sub>n</sub>aryl, optionally substituted -(CR<sup>b</sup>)<sub>n</sub>cycloalkyl, and optionally substituted -(CR<sup>b</sup>)<sub>n</sub>heterocycloalkyl;

R<sup>i</sup> is selected from the group consisting of -OH, optionally substituted -OC<sub>1</sub>-C<sub>6</sub> alkyl, -OC(O)R<sup>e</sup>, -OC(O)OR<sup>h</sup>, -F, -NHC(O)OR<sup>h</sup>, -OC(O)NH(R<sup>b</sup>), -NHC(O)R<sup>e</sup>, -NHS(=O)R<sup>e</sup>, -NHS(=O)<sub>2</sub>R<sup>e</sup>, -NHC(=S)NH(R<sup>b</sup>), and -NHC(O)NH(R<sup>b</sup>); or

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$R^3$  and  $R^5$  are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^3$  and  $R^5$  are attached, including 0 to 2 heteroatoms independently selected from  $-NR^h$ ,  $-O-$ , and  $-S-$ , with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

X is  $P(O)(YR^{11})Y''$ ;

$Y''$  is selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_6$  alkyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-CH_2OH$ , optionally substituted  $-C_2-C_6$  alkenyl, optionally substituted  $-C_2-C_6$  alkynyl, optionally substituted  $-(CR^a)_h$  cycloalkyl, optionally substituted  $(CR^a)_h$  heterocycloalkyl,  $-(CR^a)_kS(=O)R^e$ ,  $-(CR^a)_kS(=O)_2R^e$ ,  $-(CR^a)_kS(=O)_2NR^fR^g$ ,  $-(CR^a)_kC(O)NR^fR^g$ , and  $-(CR^a)_kC(O)R^e$ ;

Y is selected from the group consisting of  $-O-$ , and  $-NR^v$ ;

when Y is  $-O-$ ,  $R^{11}$  attached to  $-O-$  is selected from the group consisting of higher alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted  $CH_2$ -heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted  $-alkylaryl$ ,  $-C(R^b)_2OC(O)NR^z$ ,  $-NR^z-C(O)-R^y$ ,  $-C(R^b)_2-OC(O)R^y$ ,  $-C(R^b)_2-O-C(O)OR^y$ ,  $-C(R^b)_2OC(O)SR^y$ ,  $-alkyl-S-C(O)R^y$ ,  $-alkyl-S-S-alkylhydroxy$ , and  $-alkyl-S-S-S-alkylhydroxy$ ;

when Y is  $-NR^v$ , then  $R^{11}$  attached to  $-NR^v$  is selected from the group consisting of  $-H$ ,  $-[C(R^b)_2]_q-C(O)OR^y$ ,  $-C(R^b)_2C(O)OR^y$ ,  $-[C(R^b)_2]_q-C(O)SR^y$ , and  $-cycloalkylene-C(O)OR^y$ ;

q is an integer 2 or 3;

Each  $R^z$  is selected from the group consisting of  $R^y$  and  $-H$ ;

Each  $R^y$  is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

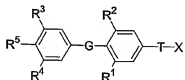
Each  $R^x$  is independently selected from the group consisting of  $-H$ , and alkyl, or together  $R^x$  and  $R^x$  form a cycloalkyl group;

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Each  $R^v$  is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxy carbonyloxyalkyl, and lower acyl;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

2. A compound of Formula I:



wherein:

G is selected from the group consisting of -O-, -S-, -Se-, -S(=O)-, -S(=O)<sub>2</sub>-, -CH<sub>2</sub>-, -CF<sub>2</sub>-, -CHF-, -C(O)-, -CH(OH)-, -NH-, and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)-, or CH<sub>2</sub> linked to any of the preceding groups;

or G is  $R^{50}$ - $R^{51}$  wherein;

$R^{50}$ - $R^{51}$  together are -C( $R^{52}$ )=C( $R^{52}$ )- or alternatively  $R^{50}$  and  $R^{51}$  are independently selected from O, S and -CH( $R^{53}$ )-, with the provisos that at least one  $R^{50}$  and  $R^{51}$  is -CH( $R^{53}$ )-, and when one of  $R^{50}$  and  $R^{51}$  is O or S, then  $R^{53}$  is  $R^{54}$ ;

$R^{54}$  is hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

$R^{53}$  is selected from hydrogen, halogen, hydroxyl, mercapto, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

$R^{52}$  is selected from hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

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T is selected from the group consisting of  $-(CR^a_2)_k$ ,  
 $-CR^b=CR^b-(CR^a_2)_n$ ,  $-(CR^a_2)_n-CR^b=CR^b$ ,  $-(CR^a_2)-CR^b=CR^b-(CR^a_2)$ ,  
 $-O(CR^b_2)(CR^a_2)_n$ ,  $-S(CR^b_2)(CR^a_2)_n$ ,  $-N(R^c)(CR^b_2)(CR^a_2)_n$ ,  
 $-N(R^b)C(O)(CR^a_2)_n$ ,  $-(CR^a_2)_mC(R^b)(NR^bR^c)$ ,  $-C(O)(CR^a_2)_m$ ,  $-(CR^a_2)_mC(O)$ ,  
 $-(CR^b_2)-O-(CR^b_2)-(CR^a_2)_p$ ,  $-(CR^b_2)-S-(CR^b_2)-(CR^a_2)_p$ ,  $-(CR^b_2)-N(R^c)-$   
 $(CR^b_2)-(CR^a_2)_p$ ,  $-(CR^a_2)_p-(CR^b_2)-O-(CR^b_2)$ ,  $-(CR^a_2)_p-$   
 $(CR^b_2)-S-(CR^b_2)$ ,  $-(CR^a_2)_p-(CR^b_2)-N(R^c)-$   
 $(CR^b_2)$  and  $-(CH_2)_pC(O)N(R^b)C(R^a_2)$ ;

k is an integer from 0-4;

m is an integer from 0-3;

n is an integer from 0-2;

p is an integer from 0-1;

Each  $R^a$  is independently selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_4$  alkyl, halogen,  $-OH$ , optionally substituted  $-O-C_1-C_4$  alkyl,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-S-C_1-C_4$  alkyl,  $-NR^bR^c$ , optionally substituted  $-C_2-C_4$  alkenyl, and optionally substituted  $-C_2-C_4$  alkynyl; with the proviso that when one  $R^a$  is attached to C through an O, S, or N atom, then the other  $R^a$  attached to the same C is a hydrogen, or attached via a carbon atom;

Each  $R^b$  is independently selected from the group consisting of hydrogen and optionally substituted  $-C_1-C_4$  alkyl;

Each  $R^c$  is independently selected from the group consisting of hydrogen and optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-C(O)-C_1-C_4$  alkyl, and  $-C(O)H$ ;

$R^1$  and  $R^2$  are each independently selected from the group consisting of halogen, optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-S-C_1-C_3$  alkyl, optionally substituted  $-C_2-C_4$  alkenyl, optionally substituted  $-C_2-C_4$  alkynyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-O-C_1-C_3$  alkyl, and cyano;

$R^3$  and  $R^4$  are each independently selected from the group consisting of hydrogen, halogen,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , cyano, optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl,

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optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^a)_m$ aryl, optionally substituted  $-(CR^a)_m$ cycloalkyl, optionally substituted  $-(CR^a)_m$ heterocycloalkyl,  $-C(R^b)=C(R^b)$ -aryl,  $-C(R^b)=C(R^b)$ -cycloalkyl,  $-C(R^b)=C(R^b)$ -heterocycloalkyl,  $-C\equiv C$ (aryl),  $-C\equiv C$ (cycloalkyl),  $-C\equiv C$ (heterocycloalkyl),  $-(CR^a)_n(CR^b)_nNR^fR^g$ ,  $-OR^d$ ,  $-SR^d$ ,  $-S(=O)R^e$ ,  $-S(=O)_2R^e$ ,  $-S(=O)_2NR^fR^g$ ,  $-C(O)NR^fR^g$ ,  $-C(O)OR^h$ ,  $-C(O)R^e$ ,  $-N(R^b)C(O)R^e$ ,  $-N(R^b)C(O)NR^fR^g$ ,  $-N(R^b)S(=O)_2R^e$ ,  $-N(R^b)S(=O)_2NR^fR^g$ , and  $-NR^fR^g$ ;

Each  $R^d$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, optionally substituted  $-(CR^b)_n$ heterocycloalkyl, and  $-C(O)NR^fR^g$ ;

Each  $R^e$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^a)_n$ aryl, optionally substituted  $-(CR^a)_n$ cycloalkyl, and optionally substituted  $-(CR^a)_n$ heterocycloalkyl;

$R^f$  and  $R^g$  are each independently selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, and optionally substituted  $-(CR^b)_n$ heterocycloalkyl, or  $R^f$  and  $R^g$  may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4 unsaturations, which may contain a second heterogroup selected from the group consisting of O,  $NR^e$ , and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally substituted  $-C_1-C_4$  alkyl,  $-OR^b$ , oxo, cyano,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ , optionally substituted phenyl, and  $-C(O)OR^h$ ;

Each  $R^h$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally

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substituted  $-(CR^b)_n$ cycloalkyl, and optionally substituted  $-(CR^b)_n$ heterocycloalkyl;

$R^5$  is selected from the group consisting of -OH, optionally substituted  $-OC_1-C_6$  alkyl,  $-OC(O)R^e$ ,  $-OC(O)OR^h$ , -F,  $-NHC(O)OR^h$ ,  $-OC(O)NH(R^h)$ ,  $-NHC(O)R^e$ ,  $-NHS(=O)R^e$ ,  $-NHS(=O)_2R^e$ ,  $-NHC(=S)NH(R^h)$ , and  $-NHC(O)NH(R^h)$ ; or

$R^3$  and  $R^5$  are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^3$  and  $R^5$  are attached, including 0 to 2 heteroatoms independently selected from  $-NR^h$ , -O-, and -S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

X is  $P(O)(YR^{11})Y''$ ;

$Y''$  is selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_6$  alkyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-CH_2OH$ , optionally substituted  $-C_2-C_6$  alkenyl, optionally substituted  $-C_2-C_6$  alkynyl, optionally substituted  $-(CR^a)_n$ cycloalkyl, optionally substituted  $(CR^a)_n$ heterocycloalkyl,  $-(CR^a)_kS(=O)R^e$ ,  $-(CR^a)_kS(=O)_2R^e$ ,  $-(CR^a)_kS(=O)_2NR^eR^e$ ,  $-(CR^a)_kC(O)NR^eR^e$ , and  $-(CR^a)_kC(O)R^e$ ;

Y is selected from the group consisting of -O-, and  $-NR^v$ ;

when Y is -O-,  $R^{11}$  attached to -O- is selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted  $CH_2$ -heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl,  $-C(R^z)_2OC(O)NR^z$ ,  $-NR^z-C(O)-R^y$ ,  $-C(R^z)_2-OC(O)R^y$ ,  $-C(R^z)_2-O-C(O)OR^y$ ,  $-C(R^z)_2OC(O)SR^y$ ,  $-alkyl-S-C(O)R^y$ ,  $-alkyl-S-S-alkylhydroxy$ , and  $-alkyl-S-S-S-alkylhydroxy$ ;

when Y is  $-NR^v$ , then  $R^{11}$  attached to  $-NR^v$  is selected from the group consisting of -H,  $-[C(R^z)_2]_q-C(O)OR^y$ ,  $-C(R^z)_2C(O)OR^y$ ,  $-[C(R^z)_2]_q-C(O)SR^y$ , and -cycloalkylene- $C(O)OR^y$ ;

q is an integer 2 or 3;

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Each  $R^z$  is selected from the group consisting of  $R^y$  and  $-H$ ;

Each  $R^y$  is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

Each  $R^x$  is independently selected from the group consisting of  $-H$ , and alkyl, or together  $R^x$  and  $R^x$  form a cycloalkyl group;

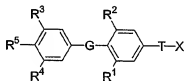
Each  $R^v$  is selected from the group consisting of  $-H$ , lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

with the proviso that:

a) when  $G$  is  $-O-$ ,  $T$  is  $-CH_2-$ ,  $R^1$  and  $R^2$  are each chloro,  $R^3$  is phenyl,  $R^4$  is hydrogen, and  $R^5$  is  $-OH$ , then  $X$  is not  $P(O)(OH)CH_3$  or  $P(O)(OCH_2CH_3)(CH_3)$ ;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

### 3. A compound of Formula I:



wherein:

$G$  is selected from the group consisting of  $-O-$ ,  $-S-$ ,  $-Se-$ ,  $-S(=O)-$ ,  $-S(=O)_2-$ ,  $-CH_2-$ ,  $-CF_2-$ ,  $-CHF-$ ,  $-C(O)-$ ,  $-CH(OH)-$ ,  $-NH-$ , and  $-N(C_1-C_4 \text{ alkyl})-$ , or  $CH_2$  linked to any of the preceding groups;

or  $G$  is  $R^{50}-R^{51}$  wherein;

$R^{50}-R^{51}$  together are  $-C(R^{52})=C(R^{53})-$  or alternatively  $R^{50}$  and  $R^{51}$  are independently selected from  $O$ ,  $S$  and  $-CH(R^{53})-$ , with the provisos that at least one  $R^{50}$  and  $R^{51}$  is  $-CH(R^{53})-$ , and when one of  $R^{50}$  and  $R^{51}$  is  $O$  or  $S$ , then  $R^{53}$  is  $R^{54}$ ;

$R^{54}$  is hydrogen, halogen,  $C_1-C_4$  alkyl,  $C_2-C_4$  alkenyl,  $C_2-C_4$  alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

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R<sup>53</sup> is selected from hydrogen, halogen, hydroxyl, mercapto, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

R<sup>52</sup> is selected from hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

T is selected from the group consisting of  $-(CR^a_2)_k-$ ,  $-CR^b=CR^b-(CR^a_2)_n-$ ,  $-(CR^a_2)_n-CR^b=CR^b-$ ,  $-(CR^a_2)-CR^b=CR^b-(CR^a_2)-$ ,  $-O(CR^b_2)(CR^a_2)_n-$ ,  $-S(CR^b_2)(CR^a_2)_n-$ ,  $-N(R^c)(CR^b_2)(CR^a_2)_n-$ ,  $-N(R^b)C(O)(CR^a_2)_n-$ ,  $-(CR^a_2)_mC(R^b)(NR^bR^c)-$ ,  $-C(O)(CR^a_2)_m-$ ,  $-(CR^a_2)_mC(O)-$ ,  $-(CR^b_2)-O-(CR^b_2)-(CR^a_2)_p-$ ,  $-(CR^b_2)-S-(CR^b_2)-(CR^a_2)_p-$ ,  $-(CR^b_2)-N(R^c)-(CR^b_2)-(CR^a_2)_p-$ ,  $-(CR^a_2)_p-(CR^b_2)-O-(CR^b_2)-$ ,  $-(CR^a_2)_p-$ ,  $(CR^b_2)-S-(CR^b_2)-$ ,  $-(CR^a_2)_p-(CR^b_2)-N(R^c)-$ ,  $(CR^b_2)-$  and  $-(CH_2)_pC(O)N(R^b)C(R^a_2)-$ ;

k is an integer from 0-4;

m is an integer from 0-3;

n is an integer from 0-2;

p is an integer from 0-1;

Each R<sup>a</sup> is independently selected from the group consisting of hydrogen, optionally substituted -C<sub>1</sub>-C<sub>4</sub> alkyl, halogen, -OH, optionally substituted -O-C<sub>1</sub>-C<sub>4</sub> alkyl, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>F, optionally substituted -S-C<sub>1</sub>-C<sub>4</sub> alkyl, -NR<sup>b</sup>R<sup>c</sup>, optionally substituted -C<sub>2</sub>-C<sub>4</sub> alkenyl, and optionally substituted -C<sub>2</sub>-C<sub>4</sub> alkynyl; with the proviso that when one R<sup>a</sup> is attached to C through an O, S, or N atom, then the other R<sup>a</sup> attached to the same C is a hydrogen, or attached via a carbon atom;

Each R<sup>b</sup> is independently selected from the group consisting of hydrogen and optionally substituted -C<sub>1</sub>-C<sub>4</sub> alkyl;



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Each  $R^c$  is independently selected from the group consisting of hydrogen and optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-C(O)-C_1-C_4$  alkyl, and  $-C(O)H$ ;

$R^1$  and  $R^2$  are each independently selected from the group consisting of halogen, optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-S-C_1-C_3$  alkyl, optionally substituted  $-C_2-C_4$  alkenyl, optionally substituted  $-C_2-C_4$  alkynyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-O-C_1-C_3$  alkyl, and cyano;

$R^3$  and  $R^4$  are each independently selected from the group consisting of hydrogen, halogen,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , cyano, optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^a)_m$ aryl, optionally substituted  $-(CR^a)_m$ cycloalkyl, optionally substituted  $-(CR^a)_m$ heterocycloalkyl,  $-C(R^b)=C(R^b)$ -aryl,  $-C(R^b)=C(R^b)$ -cycloalkyl,  $-C(R^b)=C(R^b)$ -heterocycloalkyl,  $-C\equiv C$ (aryl),  $-C\equiv C$ (cycloalkyl),  $-C\equiv C$ (heterocycloalkyl),  $-(CR^a)_m(CR^b)_nR^fR^g$ ,  $-OR^d$ ,  $-SR^d$ ,  $-S(=O)R^e$ ,  $-S(=O)_2R^e$ ,  $-S(=O)_2NR^fR^g$ ,  $-C(O)NR^fR^g$ ,  $-C(O)OR^h$ ,  $-C(O)R^e$ ,  $-N(R^b)C(O)R^e$ ,  $-N(R^b)C(O)NR^fR^g$ ,  $-N(R^b)S(=O)_2R^e$ ,  $-N(R^b)S(=O)_2NR^fR^g$ , and  $-NR^fR^g$ ;

Each  $R^d$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, optionally substituted  $-(CR^b)_n$ heterocycloalkyl, and  $-C(O)NR^fR^g$ ;

Each  $R^e$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^a)_n$ aryl, optionally substituted  $-(CR^a)_n$ cycloalkyl, and optionally substituted  $-(CR^a)_n$ heterocycloalkyl;

$R^f$  and  $R^g$  are each independently selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally

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substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, and optionally substituted  $-(CR^b)_n$ heterocycloalkyl, or  $R^f$  and  $R^g$  may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4 unsaturations, which may contain a second heterogroup selected from the group consisting of O,  $NR^e$ , and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally substituted  $-C_1-C_4$  alkyl,  $-OR^b$ , oxo, cyano,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ , optionally substituted phenyl, and  $-C(O)OR^h$ ;

Each  $R^h$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, and optionally substituted  $-(CR^b)_n$ heterocycloalkyl;

$R^5$  is selected from the group consisting of  $-OH$ , optionally substituted  $-OC_1-C_6$  alkyl,  $-OC(O)R^e$ ,  $-OC(O)OR^h$ ,  $-F$ ,  $-NHC(O)OR^h$ ,  $-OC(O)NH(R^h)$ ,  $-NHC(O)R^e$ ,  $-NHS(=O)R^e$ ,  $-NHS(=O)_2R^e$ ,  $-NHC(=S)NH(R^h)$ , and  $-NHC(O)NH(R^h)$ ; or

$R^3$  and  $R^5$  are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^3$  and  $R^5$  are attached, including 0 to 2 heteroatoms independently selected from  $-NR^b$ ,  $-O$ , and  $-S$ , with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

X is  $P(O)(YR^{11})Y''$ ;

$Y''$  is selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_6$  alkyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-CH_2OH$ , optionally substituted  $-C_2-C_6$  alkenyl, optionally substituted  $-C_2-C_6$  alkynyl, optionally substituted  $-(CR^a)_n$ cycloalkyl, optionally substituted  $(CR^a)_n$ heterocycloalkyl,  $-(CR^a)_kS(=O)R^e$ ,  $-(CR^a)_kS(=O)_2R^e$ ,  $-(CR^a)_kS(=O)_2NR^fR^g$ ,  $-(CR^a)_kC(O)NR^fR^g$ , and  $-(CR^a)_kC(O)R^e$ ;

Y is selected from the group consisting of  $-O$ -, and  $-NR^v$ ;

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when Y is -O-,  $R^{11}$  attached to -O- is selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted  $CH_2$ -heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl,  $-C(R^2)_2OC(O)NR^2$ ,  $-NR^2-C(O)-R^y$ ,  $-C(R^2)_2-OC(O)R^y$ ,  $-C(R^2)_2-O-C(O)OR^y$ ,  $-C(R^2)_2OC(O)SR^y$ , -alkyl-S-C(O)R<sup>y</sup>, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is  $-NR^y$ , then  $R^{11}$  attached to  $-NR^y$  is selected from the group consisting of -H,  $-[C(R^2)_2]_q-C(O)OR^y$ ,  $-C(R^2)_2C(O)OR^y$ ,  $-[C(R^2)_2]_q-C(O)SR^y$ , and -cycloalkylene-C(O)OR<sup>y</sup>;

q is an integer 2 or 3;

Each  $R^2$  is selected from the group consisting of  $R^y$  and -H;

Each  $R^y$  is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

Each  $R^x$  is independently selected from the group consisting of -H, and alkyl, or together  $R^x$  and  $R^x$  form a cycloalkyl group;

Each  $R^y$  is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxy-carbonyloxyalkyl, and lower acyl;

with the proviso that:

a) when G is -O-, -S-, -Se-,  $-S(=O)-$ ,  $-S(=O)_2-$ ,  $-CH_2-$ ,  $-C(O)-$ , -NH- and, T is  $-(CH_2)_{0-4}-$  or  $-C(O)NH(CR^b_2)-$ ,  $R^1$  and  $R^2$  are independently chosen from the group consisting of hydrogen, halogen, -C<sub>1</sub>-C<sub>4</sub> alkyl,  $R^3$  is  $-C(O)NR^{25}R^{26}$ ,  $-CH_2-NR^{25}R^{26}$ ,  $-NR^{25}-C(O)R^{26}$ ,  $-OR^{27}$ ,  $R^{28}$ , or



,  $R^4$  is hydrogen, halogen, cyano or alkyl, and  $R^5$  is -OH,  $R^{25}$  and  $R^{26}$  are each independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, cycloalkyl, aralkyl or heteroaralkyl,  $R^{27}$  is aryl, heteroaryl, alkyl, aralkyl, or heteroaralkyl,  $R^{28}$  is aryl, heteroaryl, or cycloalkyl,  $R^{29}$  is hydrogen, aryl, heteroaryl, alkyl, aralkyl, heteroaralkyl, then X is not  $-P(O)(OH)C_1-C_6$  alkyl or  $-P(O)(O-lower\ alkyl)C_1-C_6$  alkyl;

b) when G is -O-, -S-, -Se-,  $-S(=O)-$ ,  $-S(=O)_2-$ ,  $-CH_2-$ ,  $-CF_2-$ ,  $-C(O)-$ , -NH- and, T is  $-C(O)NH(CR^b_2)-$ ,  $R^1$  and  $R^2$  are independently

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halogen, cyano, -C<sub>1</sub>-C<sub>4</sub> alkyl, R<sup>3</sup> is halogen, -C<sub>1</sub>-C<sub>6</sub> alkyl, -C<sub>2</sub>-C<sub>6</sub> alkynyl, -C<sub>4</sub>-C<sub>7</sub> cycloalkenyl, -C<sub>3</sub>-C<sub>7</sub> cycloalkoxy, -S(=O)<sub>2</sub>(NR<sup>14</sup>R<sup>15</sup>), -N(R<sup>16</sup>)S(=O)<sub>2</sub>R<sup>17</sup>, -SR<sup>17</sup>, -S(=O)R<sup>17</sup>, -S(=O)<sub>2</sub>R<sup>17</sup>, -C(O)R<sup>16</sup>, or -CR<sup>18</sup>(OR<sup>16</sup>)R<sup>19</sup>, R<sup>4</sup> is halogen, cyano or alkyl, and R<sup>5</sup> is -OH, optionally substituted -OC<sub>1</sub>-C<sub>6</sub> alkyl, aryl or alkanoyl, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>18</sup> and R<sup>19</sup> are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroalkyl, arylalkyl, and heteroarylalkyl, or R<sup>14</sup> and R<sup>15</sup> may be joined so as to comprise a chain of 3 to 6 methylene groups to form a ring of 4 to 7-members in size, R<sup>17</sup> is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroalkyl, arylalkyl, and heteroarylalkyl, then X is not -P(O)(OH)C<sub>1</sub>-C<sub>6</sub> alkyl or -P(O)(O-lower alkyl)C<sub>1</sub>-C<sub>6</sub> alkyl;

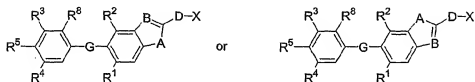
and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

4. The compound of claim 3 wherein G is -O-; T is -CH<sub>2</sub>CH(NH<sub>2</sub>)-; R<sup>1</sup> and R<sup>2</sup> are each iodo; R<sup>4</sup> is selected from the group consisting of hydrogen and iodo; R<sup>5</sup> is -OH; and R<sup>3</sup> is iodo.
5. The compound of claim 3 wherein G is -O-; T is -N(H)C(O)-; R<sup>1</sup> and R<sup>2</sup> are each methyl; R<sup>4</sup> is hydrogen; R<sup>5</sup> is -OH; and R<sup>3</sup> is -CH(OH)(4-fluorophenyl).
6. The compound of claim 3 wherein G is -CH<sub>2</sub>-; T is -OCH<sub>2</sub>-; R<sup>1</sup> and R<sup>2</sup> are each methyl; R<sup>4</sup> is hydrogen; R<sup>5</sup> is -OH; and R<sup>3</sup> is *iso*-propyl.
7. The compound of claim 3 wherein G is -O-; T is -CH<sub>2</sub>-; R<sup>1</sup> and R<sup>2</sup> are each chloro; R<sup>4</sup> is hydrogen; R<sup>5</sup> is -OH; and R<sup>3</sup> is *iso*-propyl.

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8. The compound of claim 3 wherein G is -O-; T is  $-\text{CH}_2\text{CH}_2-$ ;  $\text{R}^1$  and  $\text{R}^2$  are each chloro;  $\text{R}^4$  is hydrogen;  $\text{R}^5$  is -OH; and  $\text{R}^3$  is *iso*-propyl.

9. A compound of Formula II:



wherein:

A is selected from the group consisting of  $-\text{NR}^1$ -, -O-, and -S-;

B is selected from the group consisting of  $-\text{CR}^b$ -, and -N-;

$\text{R}^i$  is selected from the group consisting of hydrogen,  $-\text{C}(\text{O})\text{C}_1\text{-C}_4$  alkyl, and  $-\text{C}_1\text{-C}_4$  alkyl;

$\text{R}^b$  is selected from the group consisting of hydrogen and optionally substituted  $-\text{C}_1\text{-C}_4$  alkyl;

G is selected from the group consisting of -O-, -S-, -Se-,  $-\text{S}(\text{=O})$ -,  $-\text{S}(\text{=O})_2$ -,  $-\text{CH}_2$ -,  $-\text{CF}_2$ -,  $-\text{CHF}$ -,  $-\text{C}(\text{O})$ -,  $-\text{CH}(\text{OH})$ -,  $-\text{NH}$ -, and  $-\text{N}(\text{C}_1\text{-C}_4 \text{ alkyl})$ -, or  $\text{CH}_2$  linked to any of the preceding groups;

or G is  $\text{R}^{50}\text{-R}^{51}$  wherein;

$\text{R}^{50}\text{-R}^{51}$  together are  $-\text{C}(\text{R}^{52})=\text{C}(\text{R}^{52})$ - or alternatively  $\text{R}^{50}$  and  $\text{R}^{51}$  are independently selected from O, S and  $-\text{CH}(\text{R}^{53})$ -, with the provisos that at least one  $\text{R}^{50}$  and  $\text{R}^{51}$  is  $-\text{CH}(\text{R}^{53})$ -, and when one of  $\text{R}^{50}$  and  $\text{R}^{51}$  is O or S, then  $\text{R}^{53}$  is  $\text{R}^{54}$ ;

$\text{R}^{54}$  is hydrogen, halogen,  $\text{C}_1\text{-C}_4$  alkyl,  $\text{C}_2\text{-C}_4$  alkenyl,  $\text{C}_2\text{-C}_4$  alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

$\text{R}^{53}$  is selected from hydrogen, halogen, hydroxyl, mercapto,  $\text{C}_1\text{-C}_4$  alkyl,  $\text{C}_2\text{-C}_4$  alkenyl,  $\text{C}_2\text{-C}_4$  alkynyl,  $\text{C}_1\text{-C}_4$  alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy,

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trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

$R^{52}$  is selected from hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

D is selected from the group consisting of a bond,  $-(CR^a)_2$ -, and  $-C(O)-$ ;

Each  $R^a$  is independently selected from the group consisting of hydrogen, optionally substituted -C<sub>1</sub>-C<sub>4</sub> alkyl, halogen, -OH, optionally substituted -O-C<sub>1</sub>-C<sub>4</sub> alkyl, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>F, optionally substituted -S-C<sub>1</sub>-C<sub>4</sub> alkyl,  $-NR^bR^c$ , optionally substituted -C<sub>2</sub>-C<sub>4</sub> alkenyl, and optionally substituted -C<sub>2</sub>-C<sub>4</sub> alkynyl; with the proviso that when one  $R^a$  is attached to C through an O, S, or N atom, then the other  $R^a$  attached to the same C is a hydrogen, or attached via a carbon atom;

Each  $R^e$  is independently selected from the group consisting of hydrogen and optionally substituted -C<sub>1</sub>-C<sub>4</sub> alkyl, optionally substituted -C(O)-C<sub>1</sub>-C<sub>4</sub> alkyl, and -C(O)H;

$R^1$  and  $R^2$  are each independently selected from the group consisting of halogen, optionally substituted -C<sub>1</sub>-C<sub>4</sub> alkyl, optionally substituted -S-C<sub>1</sub>-C<sub>3</sub> alkyl, optionally substituted -C<sub>2</sub>-C<sub>4</sub> alkenyl, optionally substituted -C<sub>2</sub>-C<sub>4</sub> alkynyl, -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>F, optionally substituted -O-C<sub>1</sub>-C<sub>3</sub> alkyl, and cyano;

$R^8$  is selected from the group consisting of hydrogen, halogen, optionally substituted -C<sub>1</sub>-C<sub>4</sub> alkyl, optionally substituted -S-C<sub>1</sub>-C<sub>3</sub> alkyl, optionally substituted -C<sub>2</sub>-C<sub>4</sub> alkenyl, optionally substituted -C<sub>2</sub>-C<sub>4</sub> alkynyl, -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, -OCF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, optionally substituted -O-C<sub>1</sub>-C<sub>3</sub> alkyl, hydroxy,  $-(CR^a)_2$ aryl,  $-(CR^a)_2$ cycloalkyl,  $-(CR^a)_2$ heterocycloalkyl, -C(O)aryl, -C(O)cycloalkyl, -C(O)heterocycloalkyl, -C(O)alkyl and cyano;

$R^3$  and  $R^4$  are each independently selected from the group consisting of hydrogen, halogen, -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>F, cyano,

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optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^a)_m$ aryl, optionally substituted  $-(CR^a)_m$ cycloalkyl, optionally substituted  $-(CR^a)_m$ heterocycloalkyl,  $-C(R^b)=C(R^b)$ -aryl,  $-C(R^b)=C(R^b)$ -cycloalkyl,  $-C(R^b)=C(R^b)$ -heterocycloalkyl,  $-C\equiv C$ (aryl),  $-C\equiv C$ (cycloalkyl),  $-C\equiv C$ (heterocycloalkyl),  $-(CR^a)_m(CR^b)_nNR^fR^g$ ,  $-OR^d$ ,  $-SR^d$ ,  $-S(=O)R^e$ ,  $-S(=O)_2R^e$ ,  $-S(=O)_2NR^fR^g$ ,  $-C(O)NR^fR^g$ ,  $-C(O)OR^h$ ,  $-C(O)R^e$ ,  $-N(R^b)C(O)R^e$ ,  $-N(R^b)C(O)NR^fR^g$ ,  $-N(R^b)S(=O)_2R^e$ ,  $-N(R^b)S(=O)_2NR^fR^g$ , and  $-NR^fR^g$ ;

Each  $R^d$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, optionally substituted  $-(CR^b)_n$ heterocycloalkyl, and  $-C(O)NR^fR^g$ ;

Each  $R^e$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^a)_n$ aryl, optionally substituted  $-(CR^a)_n$ cycloalkyl, and optionally substituted  $-(CR^a)_n$ heterocycloalkyl;

$R^f$  and  $R^g$  are each independently selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, and optionally substituted  $-(CR^b)_n$ heterocycloalkyl, or  $R^f$  and  $R^g$  may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4 unsaturations, which may contain a second heterogroup selected from the group consisting of O,  $NR^e$ , and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally substituted  $-C_1-C_4$  alkyl,  $-OR^b$ , oxo, cyano,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ , optionally substituted phenyl, and  $-C(O)OR^h$ ;

Each  $R^h$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally

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substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, and optionally substituted  $-(CR^b)_n$ heterocycloalkyl; or

$R^3$  and  $R^8$  are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^3$  and  $R^8$  are attached, including 0 to 2 heteroatoms independently selected from  $-NR^h$ -,  $-O$ -, and  $-S$ -, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; or

$R^8$  and G are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring comprising  $-CH=CH-CH=$ ,  $-N=CH-CH=$ ,  $-CH=N-CH=$  or  $-CH=CH-N=$ ;

$R^5$  is selected from the group consisting of  $-OH$ , optionally substituted  $-OC_1-C_6$  alkyl,  $-OC(O)R^e$ ,  $-OC(O)OR^h$ ,  $-NHC(O)OR^h$ ,  $-OC(O)NH(R^h)$ ,  $-F$ ,  $-NHC(O)R^e$ ,  $-NHS(=O)R^e$ ,  $-NHS(=O)_2R^e$ ,  $-NHC(=S)NH(R^h)$ , and  $-NHC(O)NH(R^h)$ ; or

$R^3$  and  $R^5$  are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^3$  and  $R^5$  are attached, including 0 to 2 heteroatoms independently selected from  $-NR^h$ -,  $-O$ -, and  $-S$ -, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

$X$  is  $P(O)(YR^{11})Y''$ ;

$Y''$  is selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_6$  alkyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-CH_2OH$ , optionally substituted  $-C_2-C_6$  alkenyl, optionally substituted  $-C_2-C_6$  alkynyl, optionally substituted  $-(CR^a)_n$ cycloalkyl, optionally substituted  $(CR^a)_n$ heterocycloalkyl,  $-(CR^a)_kS(=O)R^e$ ,  $-(CR^a)_kS(=O)_2R^e$ ,  $-(CR^a)_kS(=O)_2NR^eR^e$ ,  $-(CR^a)_kC(O)NR^eR^e$ , and  $-(CR^a)_kC(O)R^e$ ;

$Y$  is selected from the group consisting of  $-O$ -, and  $-NR^v$ -;



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when Y is -O-,  $R^{11}$  attached to -O- is selected from the group consisting of higher alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted  $CH_2$ -heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl,  $-C(R^2)_2OC(O)NR^z_2$ ,  $-NR^2-C(O)-R^y$ ,  $-C(R^2)_2-OC(O)R^y$ ,  $-C(R^2)_2-O-C(O)OR^y$ ,  $-C(R^2)_2OC(O)SR^y$ , -alkyl-S-C(O) $R^y$ , -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-alkylhydroxy;

when Y is  $-NR^v$ , then  $R^{11}$  attached to  $-NR^v$  is selected from the group consisting of -H,  $-[C(R^2)_2]_q-C(O)OR^y$ ,  $-C(R^2)_2C(O)OR^y$ ,  $-[C(R^2)_2]_q-C(O)SR^y$ , and -cycloalkylene-C(O) $OR^y$ ;

q is an integer 2 or 3;

Each  $R^z$  is selected from the group consisting of  $R^y$  and -H;

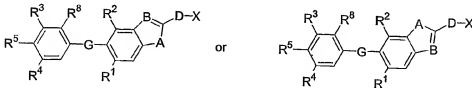
Each  $R^y$  is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

Each  $R^x$  is independently selected from the group consisting of -H, and alkyl, or together  $R^x$  and  $R^x$  form a cycloalkyl group;

Each  $R^v$  is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

10. A compound of Formula II:



wherein:

A is selected from the group consisting of  $-NR^i$ -, -O-, and -S-;

B is selected from the group consisting of  $-CR^b$ -, and -N-;

$R^i$  is selected from the group consisting of hydrogen,  $-C(O)C_1-C_4$  alkyl, and  $-C_1-C_4$  alkyl;

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R<sup>b</sup> is selected from the group consisting of hydrogen and optionally substituted -C<sub>1</sub>-C<sub>4</sub> alkyl;

G is selected from the group consisting of -O-, -S-, -Se-, -S(=O)-, -S(=O)<sub>2</sub>-, -CH<sub>2</sub>-, -CF<sub>2</sub>-, -CHF-, -C(O)-, -CH(OH)-, -NH-, and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)-, or CH<sub>2</sub> linked to any of the preceding groups;

or G is R<sup>50</sup>-R<sup>51</sup> wherein;

R<sup>50</sup>-R<sup>51</sup> together are -C(R<sup>52</sup>)=C(R<sup>52</sup>)- or alternatively R<sup>50</sup> and R<sup>51</sup> are independently selected from O, S and -CH(R<sup>53</sup>)-, with the provisos that at least one R<sup>50</sup> and R<sup>51</sup> is -CH(R<sup>53</sup>)-, and when one of R<sup>50</sup> and R<sup>51</sup> is O or S, then R<sup>53</sup> is R<sup>54</sup>;

R<sup>54</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

R<sup>53</sup> is selected from hydrogen, halogen, hydroxyl, mercapto, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

R<sup>52</sup> is selected from hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

D is selected from the group consisting of a bond, -(CR<sup>a</sup>)<sub>2</sub>-, and -C(O)-;

Each R<sup>a</sup> is independently selected from the group consisting of hydrogen, optionally substituted -C<sub>1</sub>-C<sub>4</sub> alkyl, halogen, -OH, optionally substituted -O-C<sub>1</sub>-C<sub>4</sub> alkyl, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>F, optionally substituted -S-C<sub>1</sub>-C<sub>4</sub> alkyl, -NR<sup>b</sup>R<sup>c</sup>, optionally substituted -C<sub>2</sub>-C<sub>4</sub> alkenyl, and optionally substituted -C<sub>2</sub>-C<sub>4</sub> alkynyl; with the proviso that when one R<sup>a</sup> is attached to C through an O, S, or N atom, then the other R<sup>a</sup> attached to the same C is a hydrogen, or attached via a carbon atom;

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Each  $R^e$  is independently selected from the group consisting of hydrogen and optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-C(O)-C_1-C_4$  alkyl, and  $-C(O)H$ ;

$R^1$  and  $R^2$  are each independently selected from the group consisting of halogen, optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-S-C_1-C_3$  alkyl, optionally substituted  $-C_2-C_4$  alkenyl, optionally substituted  $-C_2-C_4$  alkynyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-O-C_1-C_3$  alkyl, and cyano;

$R^8$  is selected from the group consisting of hydrogen, halogen, optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-S-C_1-C_3$  alkyl, optionally substituted  $-C_2-C_4$  alkenyl, optionally substituted  $-C_2-C_4$  alkynyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-O-C_1-C_3$  alkyl, hydroxy,  $-(CR^a)_2$ aryl,  $-(CR^a)_2$ cycloalkyl,  $-(CR^a)_2$ heterocycloalkyl,  $-C(O)$ aryl,  $-C(O)$ cycloalkyl,  $-C(O)$ heterocycloalkyl,  $-C(O)$ alkyl and cyano;

$R^3$  and  $R^4$  are each independently selected from the group consisting of hydrogen, halogen,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , cyano, optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^a)_m$ aryl, optionally substituted  $-(CR^a)_m$ cycloalkyl, optionally substituted  $-(CR^a)_m$ heterocycloalkyl,  $-C(R^b)=C(R^b)$ -aryl,  $-C(R^b)=C(R^b)$ -cycloalkyl,  $-C(R^b)=C(R^b)$ -heterocycloalkyl,  $-C\equiv C$ (aryl),  $-C\equiv C$ (cycloalkyl),  $-C\equiv C$ (heterocycloalkyl),  $-(CR^a)_n(CR^b)_2NR^fR^g$ ,  $-OR^d$ ,  $-SR^d$ ,  $-S(=O)R^e$ ,  $-S(=O)_2R^e$ ,  $-S(=O)_2NR^fR^g$ ,  $-C(O)NR^fR^g$ ,  $-C(O)OR^h$ ,  $-C(O)R^e$ ,  $-N(R^b)C(O)R^e$ ,  $-N(R^b)C(O)NR^fR^g$ ,  $-N(R^b)S(=O)_2R^e$ ,  $-N(R^b)S(=O)_2NR^fR^g$ , and  $-NR^fR^g$ ;

Each  $R^d$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, optionally substituted  $-(CR^b)_n$ heterocycloalkyl, and  $-C(O)NR^fR^g$ ;

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Each  $R^c$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^a_2)_n$ aryl, optionally substituted  $-(CR^a_2)_n$ cycloalkyl, and optionally substituted  $-(CR^a_2)_n$ heterocycloalkyl;

$R^f$  and  $R^g$  are each independently selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b_2)_n$ aryl, optionally substituted  $-(CR^b_2)_n$ cycloalkyl, and optionally substituted  $-(CR^b_2)_n$ heterocycloalkyl, or  $R^f$  and  $R^g$  may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4 unsaturations, which may contain a second heterogroup selected from the group consisting of O,  $NR^c$ , and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally substituted  $-C_1-C_4$  alkyl,  $-OR^b$ , oxo, cyano,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ , optionally substituted phenyl, and  $-C(O)OR^b$ ;

Each  $R^h$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b_2)_n$ aryl, optionally substituted  $-(CR^b_2)_n$ cycloalkyl, and optionally substituted  $-(CR^b_2)_n$ heterocycloalkyl; or

$R^3$  and  $R^8$  are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^3$  and  $R^8$  are attached, including 0 to 2 heteroatoms independently selected from  $-NR^h$ ,  $-O$ , and  $-S$ , with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; or

$R^8$  and G are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring comprising  $-CH=CH-CH=$ ,  $-N=CH-CH=$ ,  $-CH=N-CH=$  or  $-CH=CH-N=$ ;

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$R^5$  is selected from the group consisting of -OH, optionally substituted  $-OC_1-C_6$  alkyl,  $-OC(O)R^e$ ,  $-OC(O)OR^h$ ,  $-NHC(O)OR^h$ ,  $-OC(O)NH(R^h)$ , -F,  $-NHC(O)R^e$ ,  $-NHS(=O)R^e$ ,  $-NHS(=O)_2R^e$ ,  $-NHC(=S)NH(R^h)$ , and  $-NHC(O)NH(R^h)$ ; or

$R^3$  and  $R^5$  are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^3$  and  $R^5$  are attached, including 0 to 2 heteroatoms independently selected from  $-NR^h$ , -O-, and -S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

X is  $P(O)(YR^{11})Y''$ ;

$Y''$  is selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_6$  alkyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-CH_2OH$ , optionally substituted  $-C_2-C_6$  alkenyl, optionally substituted  $-C_2-C_6$  alkynyl, optionally substituted  $-(CR^a)_n$ cycloalkyl, optionally substituted  $(CR^a)_n$ heterocycloalkyl,  $-(CR^a)_kS(=O)R^e$ ,  $-(CR^a)_kS(=O)_2R^e$ ,  $-(CR^a)_kS(=O)_2NR^fR^g$ ,  $-(CR^a)_kC(O)NR^fR^g$ , and  $-(CR^a)_kC(O)R^e$ ;

Y is selected from the group consisting of -O-, and  $-NR^v$ ;

when Y is -O-,  $R^{11}$  attached to -O- is selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted  $CH_2$ -heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl,  $-C(R^b)_2OC(O)NR^z$ ,  $-NR^z-C(O)-R^y$ ,  $-C(R^b)_2-OC(O)R^y$ ,  $-C(R^b)_2-O-C(O)OR^y$ ,  $-C(R^b)_2OC(O)SR^y$ , -alkyl-S-C(O)R<sup>y</sup>, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is  $-NR^v$ , then  $R^{11}$  attached to  $-NR^v$  is selected from the group consisting of -H,  $-[C(R^b)_2]_q-C(O)OR^y$ ,  $-C(R^b)_2C(O)OR^y$ ,  $-[C(R^b)_2]_q-C(O)SR^y$ , and -cycloalkylene-C(O)OR<sup>y</sup>;

q is an integer 2 or 3;

Each  $R^z$  is selected from the group consisting of  $R^y$  and -H;

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Each  $R^y$  is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

Each  $R^x$  is independently selected from the group consisting of -H, and alkyl, or together  $R^x$  and  $R^x$  form a cycloalkyl group;

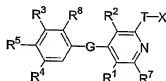
Each  $R^y$  is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

11. The compound of claim 9 or 10 wherein D is selected from the group consisting of a bond and  $-CH_2-$ .
12. The compound of claim 11 wherein D is a bond.
13. The compound of claim 9 or 10 wherein A is selected from the group consisting of -NH-, -NMe-, -O-, and -S-.
14. The compound of claim 9 or 10 wherein B is selected from the group consisting of -CH-, -CMe-, and -N-.
15. The compound of claim 9 or 10 wherein G is -O-; D is a bond; A is selected from the group consisting of -NH- and -NMe-; B is selected from the group consisting of -CH- and -CMe-;  $R^1$  and  $R^2$  are each bromo;  $R^4$  is selected from the group consisting of hydrogen and iodo;  $R^5$  is -OH; and  $R^3$  is isopropyl or 4-fluorobenzyl.

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16. The compound of claim 9 or 10 wherein G is -O-; D is a bond; A is -O-; B is selected from the group consisting of -CH- and -CMe-; R<sup>1</sup> and R<sup>2</sup> are each bromo; R<sup>4</sup> is selected from the group consisting of hydrogen and iodo; R<sup>5</sup> is -OH; and R<sup>3</sup> is isopropyl or 4-fluorobenzyl.
17. A compound of Formula III:



wherein

G is selected from the group consisting of -O-, -S-, -Se-, -S(=O)-, -S(=O)<sub>2</sub>-, -CH<sub>2</sub>-, -CF<sub>2</sub>-, -CHF-, -C(O)-, -CH(OH)-, -NH-, and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)-, or CH<sub>2</sub> linked to any of the preceding groups;

or G is R<sup>50</sup>-R<sup>51</sup> wherein;

R<sup>50</sup>-R<sup>51</sup> together are -C(R<sup>52</sup>)=C(R<sup>52</sup>)- or alternatively R<sup>50</sup> and R<sup>51</sup> are independently selected from O, S and -CH(R<sup>53</sup>)-, with the provisos that at least one R<sup>50</sup> and R<sup>51</sup> is -CH(R<sup>53</sup>)-, and when one of R<sup>50</sup> and R<sup>51</sup> is O or S, then R<sup>53</sup> is R<sup>54</sup>;

R<sup>54</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

R<sup>53</sup> is selected from hydrogen, halogen, hydroxyl, mercapto, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

R<sup>52</sup> is selected from hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

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T is selected from the group consisting of  $-(CR^a)_k-$ ,  $-CR^b=CR^b-(CR^a)_n-$ ,  $-(CR^a)_n-CR^b=CR^b-$ ,  $-(CR^a)_2-CR^b=CR^b-(CR^a)_2-$ ,  $-O(CR^b_2)(CR^a)_n-$ ,  $-S(CR^b_2)(CR^a)_n-$ ,  $-N(R^c)(CR^b_2)(CR^a)_n-$ ,  $-N(R^b)C(O)(CR^a)_n-$ ,  $-(CR^a)_mC(R^b)(NR^bR^c)-$ ,  $-C(O)(CR^a)_m-$ ,  $-(CR^a)_mC(O)-$ ,  $-(CR^b_2)-O-(CR^b_2)-(CR^a)_p-$ ,  $-(CR^b_2)-S-(CR^b_2)-(CR^a)_p-$ ,  $-(CR^b_2)-N(R^c)-(CR^b_2)-(CR^a)_p-$ ,  $-(CR^a)_p-(CR^b_2)-O-(CR^b_2)-$ ,  $-(CR^a)_p-(CR^b_2)-S-(CR^b_2)-$ ,  $-(CR^a)_p-(CR^b_2)-N(R^c)-(CR^b_2)-$ ,  $-(CH_2)_pC(O)N(R^b)C(R^a)_2-$ ,  $-(CR^a)_nC(R^b_2)O-$ ,  $-(CR^a)_nC(R^b_2)N(R^b)-$ ,  $-(CR^a)_nC(R^b_2)S-$ ,  $-C(O)(CR^a)_pC(R^b_2)O-$ ,  $-C(O)(CR^a)_pC(R^b_2)N(R^b)-$ ,  $-C(O)(CR^a)_pC(R^b_2)S-$ ,  $-(CR^a)_pC(O)C(R^b_2)O-$ ,  $-(CR^a)_pC(O)C(R^b_2)N(R^b)-$ , and  $-(CR^a)_pC(O)C(R^b_2)S-$ ;

k is an integer from 0-4;

m is an integer from 0-3;

n is an integer from 0-2;

p is an integer from 0-1;

Each  $R^a$  is independently selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_4$  alkyl, halogen,  $-OH$ , optionally substituted  $-O-C_1-C_4$  alkyl,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-S-C_1-C_4$  alkyl,  $-NR^bR^c$ , optionally substituted  $-C_2-C_4$  alkenyl, and optionally substituted  $-C_2-C_4$  alkynyl; with the proviso that when one  $R^a$  is attached to C through an O, S, or N atom, then the other  $R^a$  attached to the same C is a hydrogen, or attached via a carbon atom;

Each  $R^b$  is independently selected from the group consisting of hydrogen and optionally substituted  $-C_1-C_4$  alkyl;

Each  $R^c$  is independently selected from the group consisting of hydrogen and optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-C(O)-C_1-C_4$  alkyl, and  $-C(O)H$ ;

$R^1$  and  $R^2$  are each independently selected from the group consisting of halogen, optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-S-C_1-C_3$  alkyl, optionally substituted  $-C_2-C_4$  alkenyl, optionally substituted  $-C_2-C_4$  alkynyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-O-C_1-C_3$  alkyl, and cyano;



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$R^8$  is selected from the group consisting of hydrogen, halogen, optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-S-C_1-C_3$  alkyl, optionally substituted  $-C_2-C_4$  alkenyl, optionally substituted  $-C_2-C_4$  alkynyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-O-C_1-C_3$  alkyl, hydroxy,  $(CR^a)_2$ aryl,  $-(CR^a)_2$ cycloalkyl,  $-(CR^a)_2$ heterocycloalkyl,  $-C(O)$ aryl,  $-C(O)$ cycloalkyl,  $-C(O)$ heterocycloalkyl,  $-C(O)$ alkyl and cyano;

$R^3$  and  $R^4$  are each independently selected from the group consisting of hydrogen, halogen,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , cyano, optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^a)_2$ aryl, optionally substituted  $-(CR^a)_2$ cycloalkyl, optionally substituted  $-(CR^a)_2$ heterocycloalkyl,  $-C(R^b)=C(R^b)$ -aryl,  $-C(R^b)=C(R^b)$ -cycloalkyl,  $-C(R^b)=C(R^b)$ -heterocycloalkyl,  $-C\equiv C$ (aryl),  $-C\equiv C$ (cycloalkyl),  $-C\equiv C$ (heterocycloalkyl),  $-(CR^a)_2$  $(CR^b)_2$  $NR^fR^g$ ,  $-OR^d$ ,  $-SR^d$ ,  $-S(O)R^e$ ,  $-S(O)_2R^e$ ,  $-S(O)_2NR^fR^g$ ,  $-C(O)NR^fR^g$ ,  $-C(O)OR^h$ ,  $-C(O)R^e$ ,  $-N(R^b)C(O)R^e$ ,  $-N(R^b)C(O)NR^fR^g$ ,  $-N(R^b)S(O)_2R^e$ ,  $-N(R^b)S(O)_2NR^fR^g$ , and  $-NR^fR^g$ ;

Each  $R^d$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_2$ aryl, optionally substituted  $-(CR^b)_2$ cycloalkyl, optionally substituted  $-(CR^b)_2$ heterocycloalkyl, and  $-C(O)NR^fR^g$ ;

Each  $R^e$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^a)_2$ aryl, optionally substituted  $-(CR^a)_2$ cycloalkyl, and optionally substituted  $-(CR^a)_2$ heterocycloalkyl;

$R^f$  and  $R^g$  are each independently selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_2$ aryl, optionally substituted  $-(CR^b)_2$ cycloalkyl, and

optionally substituted  $-(CR^b_2)_n$  heterocycloalkyl, or  $R^f$  and  $R^g$  may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4 unsaturations, which may contain a second heterogroup selected from the group consisting of O,  $NR^e$ , and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally substituted  $-C_1-C_4$  alkyl,  $-OR^b$ , oxo, cyano,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ , optionally substituted phenyl, and  $-C(O)OR^h$ ;

Each  $R^h$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b_2)_n$  aryl, optionally substituted  $-(CR^b_2)_n$  cycloalkyl, and optionally substituted  $-(CR^b_2)_n$  heterocycloalkyl; or

$R^3$  and  $R^8$  are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^3$  and  $R^8$  are attached, including 0 to 2 heteroatoms independently selected from  $-NR^h$ ,  $-O-$ , and  $-S-$ , with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; or

$R^8$  and G are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring comprising  $-CH=CH-CH=$ ,  $-N=CH-CH=$ ,  $-CH=N-CH=$  or  $-CH=CH-N=$ ;

$R^5$  is selected from the group consisting of  $-OH$ , optionally substituted  $-OC_1-C_6$  alkyl,  $-OC(O)R^e$ ,  $-OC(O)OR^h$ ,  $-NHC(O)OR^h$ ,  $-OC(O)NH(R^h)$ ,  $-F$ ,  $-NHC(O)R^e$ ,  $-NHS(=O)R^e$ ,  $-NHS(=O)_2R^e$ ,  $-NHC(=S)NH(R^h)$ , and  $-NHC(O)NH(R^h)$ ; or

$R^3$  and  $R^5$  are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^3$  and  $R^5$  are attached, including 0 to 2 heteroatoms independently selected from  $-NR^h$ ,  $-O-$ , and  $-S-$ , with the proviso that when there are 2 heteroatoms in the ring and both

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heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

$R^7$  is selected from the group consisting of hydrogen, halogen, amino, hydroxyl,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ ,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ , cyano,  $-O-C_1-C_4$  alkyl,  $-SH$  and  $-S-C_1-C_4$  alkyl;

$X$  is  $P(O)(YR^{11})Y''$ ;

$Y''$  is selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_6$ -alkyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-CH_2OH$ , optionally substituted  $-C_2-C_6$  alkenyl, optionally substituted  $-C_2-C_6$  alkynyl, optionally substituted  $-(CR^2)_n$  cycloalkyl, optionally substituted  $(CR^2)_n$  heterocycloalkyl,  $-(CR^2)_kS(=O)R^e$ ,  $-(CR^2)_kS(=O)_2R^e$ ,  $-(CR^2)_kS(=O)_2NR^fR^g$ ,  $-(CR^2)_kC(O)NR^fR^g$ , and  $-(CR^2)_kC(O)R^e$ ;

$Y$  is selected from the group consisting of  $-O-$ , and  $-NR^v$ ;

when  $Y$  is  $-O-$ ,  $R^{11}$  attached to  $-O-$  is selected from the group consisting of higher alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted  $CH_2$ -heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted  $-alkylaryl$ ,  $-C(R^3)_2OC(O)NR^z$ ,  $-NR^z-C(O)-R^y$ ,  $-C(R^3)_2-OC(O)R^y$ ,  $-C(R^3)_2-O-C(O)OR^y$ ,  $-C(R^3)_2OC(O)SR^y$ ,  $-alkyl-S-C(O)R^y$ ,  $-alkyl-S-S-alkylhydroxy$ , and  $-alkyl-S-S-alkylhydroxy$ ;

when  $Y$  is  $-NR^v$ , then  $R^{11}$  attached to  $-NR^v$  is selected from the group consisting of  $-H$ ,  $-[C(R^3)_2]_q-C(O)OR^y$ ,  $-C(R^3)_2C(O)OR^y$ ,  $-[C(R^3)_2]_q-C(O)SR^y$ , and  $-cycloalkylene-C(O)OR^y$ ;

$q$  is an integer 2 or 3;

Each  $R^z$  is selected from the group consisting of  $R^y$  and  $-H$ ;

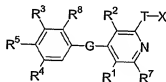
Each  $R^y$  is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

Each  $R^x$  is independently selected from the group consisting of  $-H$ , and alkyl, or together  $R^x$  and  $R^x$  form a cycloalkyl group;

Each  $R^v$  is selected from the group consisting of  $-H$ , lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

18. A compound of Formula III:



wherein

G is selected from the group consisting of -O-, -S-, -Se-, -S(=O)-, -S(=O)<sub>2</sub>-, -CH<sub>2</sub>-, -CF<sub>2</sub>-, -CHF-, -C(O)-, -CH(OH)-, -NH-, and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)-, or CH<sub>2</sub> linked to any of the preceding groups;

or G is R<sup>50</sup>R<sup>51</sup> wherein;

R<sup>50</sup>-R<sup>51</sup> together are -C(R<sup>52</sup>)=C(R<sup>52</sup>)- or alternatively R<sup>50</sup> and R<sup>51</sup> are independently selected from O, S and -CH(R<sup>53</sup>)-, with the provisos that at least one R<sup>50</sup> and R<sup>51</sup> is -CH(R<sup>53</sup>)-, and when one of R<sup>50</sup> and R<sup>51</sup> is O or S, then R<sup>53</sup> is R<sup>54</sup>;

R<sup>54</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

R<sup>53</sup> is selected from hydrogen, halogen, hydroxyl, mercapto, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

R<sup>52</sup> is selected from hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

T is selected from the group consisting of -(CR<sup>a</sup><sub>2</sub>)<sub>k</sub>-, -CR<sup>b</sup>=CR<sup>b</sup>-(CR<sup>a</sup><sub>2</sub>)<sub>n</sub>-, -(CR<sup>a</sup><sub>2</sub>)<sub>n</sub>-CR<sup>b</sup>=CR<sup>b</sup>-, -(CR<sup>a</sup><sub>2</sub>)<sub>n</sub>-CR<sup>b</sup>=CR<sup>b</sup>-(CR<sup>a</sup><sub>2</sub>)<sub>n</sub>-, -O(CR<sup>b</sup><sub>2</sub>)(CR<sup>a</sup><sub>2</sub>)<sub>n</sub>-, -S(CR<sup>b</sup><sub>2</sub>)(CR<sup>a</sup><sub>2</sub>)<sub>n</sub>-, -N(R<sup>c</sup>)(CR<sup>b</sup><sub>2</sub>)(CR<sup>a</sup><sub>2</sub>)<sub>n</sub>-,

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$-N(R^b)C(O)(CR^a_2)_n-$ ,  $-(CR^a_2)_mC(R^b)(NR^bR^c)-$ ,  $-C(O)(CR^a_2)_m-$ ,  $-(CR^a_2)_mC(O)-$ ,  
 $-(CR^b_2)-O-(CR^b_2)-(CR^a_2)_p-$ ,  $-(CR^b_2)-S-(CR^b_2)-(CR^a_2)_p-$ ,  $-(CR^b_2)-N(R^b)-$   
 $(CR^b_2)-(CR^a_2)_p-$ ,  $-(CR^a_2)_p-(CR^b_2)-O-(CR^b_2)-$ ,  $-(CR^a_2)_p-$   
 $(CR^b_2)-S-(CR^b_2)-$ ,  $-(CR^a_2)_p-(CR^b_2)-N(R^b)-$   
 $(CR^b_2)-$   $-(CH_2)_pC(O)N(R^b)C(R^a_2)-$ ,  $-(CR^a_2)_pC(R^b_2)O-$ ,  
 $-(CR^a_2)_nC(R^b_2)N(R^b)-$ ,  $-(CR^a_2)_nC(R^b_2)S-$ ,  $-C(O)(CR^a_2)_pC(R^b_2)O-$ ,  
 $-C(O)(CR^a_2)_pC(R^b_2)N(R^b)-$ ,  $-C(O)(CR^a_2)_pC(R^b_2)S-$ ,  $-(CR^a_2)_pC(O)C(R^b_2)O-$ ,  
 $-(CR^a_2)_pC(O)C(R^b_2)N(R^b)-$ , and  $-(CR^a_2)_pC(O)C(R^b_2)S-$ ;

$k$  is an integer from 0-4;

$m$  is an integer from 0-3;

$n$  is an integer from 0-2;

$p$  is an integer from 0-1;

Each  $R^a$  is independently selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_4$  alkyl, halogen,  $-OH$ , optionally substituted  $-O-C_1-C_4$  alkyl,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-S-C_1-C_4$  alkyl,  $-NR^bR^c$ , optionally substituted  $-C_2-C_4$  alkenyl, and optionally substituted  $-C_2-C_4$  alkynyl; with the proviso that when one  $R^a$  is attached to  $C$  through an O, S, or N atom, then the other  $R^a$  attached to the same  $C$  is a hydrogen, or attached via a carbon atom;

Each  $R^b$  is independently selected from the group consisting of hydrogen and optionally substituted  $-C_1-C_4$  alkyl;

Each  $R^c$  is independently selected from the group consisting of hydrogen and optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-C(O)-C_1-C_4$  alkyl, and  $-C(O)H$ ;

$R^1$  and  $R^2$  are each independently selected from the group consisting of halogen, optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-S-C_1-C_3$  alkyl, optionally substituted  $-C_2-C_4$  alkenyl, optionally substituted  $-C_2-C_4$  alkynyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-O-C_1-C_3$  alkyl, and cyano;

$R^8$  is selected from the group consisting of hydrogen, halogen, optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-S-C_1-C_3$  alkyl, optionally substituted  $-C_2-C_4$  alkenyl, optionally substituted  $-C_2-C_4$

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alkynyl,  $-\text{CF}_3$ ,  $-\text{CHF}_2$ ,  $-\text{CH}_2\text{F}$ ,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{F}$ , optionally substituted  $-\text{O}-\text{C}_1-\text{C}_3$  alkyl, hydroxy,  $(\text{CR}^a)_2\text{aryl}$ ,  $(\text{CR}^a)_2\text{cycloalkyl}$ ,  $(\text{CR}^a)_2\text{heterocycloalkyl}$ ,  $-\text{C}(\text{O})\text{aryl}$ ,  $-\text{C}(\text{O})\text{cycloalkyl}$ ,  $-\text{C}(\text{O})\text{heterocycloalkyl}$ ,  $-\text{C}(\text{O})\text{alkyl}$  and cyano;

$\text{R}^3$  and  $\text{R}^4$  are each independently selected from the group consisting of hydrogen, halogen,  $-\text{CF}_3$ ,  $-\text{CHF}_2$ ,  $-\text{CH}_2\text{F}$ ,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{F}$ , cyano, optionally substituted  $-\text{C}_1-\text{C}_{12}$  alkyl, optionally substituted  $-\text{C}_2-\text{C}_{12}$  alkenyl, optionally substituted  $-\text{C}_2-\text{C}_{12}$  alkynyl, optionally substituted  $(\text{CR}^a)_m\text{aryl}$ , optionally substituted  $(\text{CR}^a)_m\text{cycloalkyl}$ , optionally substituted  $(\text{CR}^a)_m\text{heterocycloalkyl}$ ,  $-\text{C}(\text{R}^b)=\text{C}(\text{R}^b)\text{-aryl}$ ,  $-\text{C}(\text{R}^b)=\text{C}(\text{R}^b)\text{-cycloalkyl}$ ,  $-\text{C}(\text{R}^b)=\text{C}(\text{R}^b)\text{-heterocycloalkyl}$ ,  $-\text{C}\equiv\text{C}(\text{aryl})$ ,  $-\text{C}\equiv\text{C}(\text{cycloalkyl})$ ,  $-\text{C}\equiv\text{C}(\text{heterocycloalkyl})$ ,  $(\text{CR}^a)_n(\text{CR}^b)_n\text{NR}^f\text{R}^g$ ,  $-\text{OR}^d$ ,  $-\text{SR}^d$ ,  $-\text{S}(=\text{O})\text{R}^e$ ,  $-\text{S}(=\text{O})_2\text{R}^e$ ,  $-\text{S}(=\text{O})_2\text{NR}^f\text{R}^g$ ,  $-\text{C}(\text{O})\text{NR}^f\text{R}^g$ ,  $-\text{C}(\text{O})\text{OR}^h$ ,  $-\text{C}(\text{O})\text{R}^e$ ,  $-\text{N}(\text{R}^b)\text{C}(\text{O})\text{R}^e$ ,  $-\text{N}(\text{R}^b)\text{C}(\text{O})\text{NR}^f\text{R}^g$ ,  $-\text{N}(\text{R}^b)\text{S}(=\text{O})_2\text{R}^e$ ,  $-\text{N}(\text{R}^b)\text{S}(=\text{O})_2\text{NR}^f\text{R}^g$ , and  $-\text{NR}^f\text{R}^g$ ;

Each  $\text{R}^d$  is selected from the group consisting of optionally substituted  $-\text{C}_1-\text{C}_{12}$  alkyl, optionally substituted  $-\text{C}_2-\text{C}_{12}$  alkenyl, optionally substituted  $-\text{C}_2-\text{C}_{12}$  alkynyl, optionally substituted  $(\text{CR}^b)_n\text{aryl}$ , optionally substituted  $(\text{CR}^b)_n\text{cycloalkyl}$ , optionally substituted  $(\text{CR}^b)_n\text{heterocycloalkyl}$ , and  $-\text{C}(\text{O})\text{NR}^f\text{R}^g$ ;

Each  $\text{R}^e$  is selected from the group consisting of optionally substituted  $-\text{C}_1-\text{C}_{12}$  alkyl, optionally substituted  $-\text{C}_2-\text{C}_{12}$  alkenyl, optionally substituted  $-\text{C}_2-\text{C}_{12}$  alkynyl, optionally substituted  $(\text{CR}^a)_n\text{aryl}$ , optionally substituted  $(\text{CR}^a)_n\text{cycloalkyl}$ , and optionally substituted  $(\text{CR}^a)_n\text{heterocycloalkyl}$ ;

$\text{R}^f$  and  $\text{R}^g$  are each independently selected from the group consisting of hydrogen, optionally substituted  $-\text{C}_1-\text{C}_{12}$  alkyl, optionally substituted  $-\text{C}_2-\text{C}_{12}$  alkenyl, optionally substituted  $-\text{C}_2-\text{C}_{12}$  alkynyl, optionally substituted  $(\text{CR}^b)_n\text{aryl}$ , optionally substituted  $(\text{CR}^b)_n\text{cycloalkyl}$ , and optionally substituted  $(\text{CR}^b)_n\text{heterocycloalkyl}$ , or  $\text{R}^f$  and  $\text{R}^g$  may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4 unsaturations, which may contain a second heterogroup selected from the

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group consisting of O, NR<sup>c</sup>, and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally substituted -C<sub>1</sub>-C<sub>4</sub> alkyl, -OR<sup>b</sup>, oxo, cyano, -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, optionally substituted phenyl, and -C(O)OR<sup>b</sup>;

Each R<sup>b</sup> is selected from the group consisting of optionally substituted -C<sub>1</sub>-C<sub>12</sub> alkyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkenyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkynyl, optionally substituted -(CR<sup>b</sup>)<sub>n</sub>aryl, optionally substituted -(CR<sup>b</sup>)<sub>n</sub>cycloalkyl, and optionally substituted -(CR<sup>b</sup>)<sub>n</sub>heterocycloalkyl; or

R<sup>3</sup> and R<sup>8</sup> are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which R<sup>3</sup> and R<sup>8</sup> are attached, including 0 to 2 heteroatoms independently selected from -NR<sup>h</sup>, -O-, and -S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; or

R<sup>8</sup> and G are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring comprising -CH=CH-CH=, -N=CH-CH=, -CH=N-CH= or -CH=CH-N=;

R<sup>5</sup> is selected from the group consisting of -OH, optionally substituted -OC<sub>1</sub>-C<sub>6</sub> alkyl, -OC(O)R<sup>c</sup>, -OC(O)OR<sup>b</sup>, -NHC(O)OR<sup>b</sup>, -OC(O)NH(R<sup>b</sup>), -F, -NHC(O)R<sup>c</sup>, -NHS(=O)R<sup>c</sup>, -NHS(=O)<sub>2</sub>R<sup>c</sup>, -NHC(=S)NH(R<sup>b</sup>), and -NHC(O)NH(R<sup>b</sup>); or

R<sup>3</sup> and R<sup>5</sup> are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which R<sup>3</sup> and R<sup>5</sup> are attached, including 0 to 2 heteroatoms independently selected from -NR<sup>h</sup>, -O-, and -S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

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$R^7$  is selected from the group consisting of hydrogen, halogen, amino, hydroxyl,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ ,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ , cyano,  $-O-C_1-C_4$  alkyl,  $-SH$  and  $-S-C_1-C_4$  alkyl;

$X$  is  $P(O)(YR^{11})Y''$ ;

$Y''$  is selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_6$ -alkyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-CH_2OH$ , optionally substituted  $-C_2-C_6$  alkenyl, optionally substituted  $-C_2-C_6$  alkynyl, optionally substituted  $-(CR^a)_2$ cycloalkyl, optionally substituted  $(CR^a)_2$ heterocycloalkyl,  $-(CR^a)_kS(=O)R^e$ ,  $-(CR^a)_kS(=O)_2R^e$ ,  $-(CR^a)_kS(=O)_2NR^fR^g$ ,  $-(CR^a)_kC(O)NR^fR^g$ , and  $-(CR^a)_kC(O)R^e$ ;

$Y$  is selected from the group consisting of  $-O-$ , and  $-NR^v$ ;

when  $Y$  is  $-O-$ ,  $R^{11}$  attached to  $-O-$  is selected from the group consisting of  $-H$ , alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted  $CH_2$ -heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted  $-alkylaryl$ ,  $-C(R^2)_2OC(O)NR^z$ ,  $-NR^z-C(O)-R^y$ ,  $-C(R^2)_2OC(O)R^y$ ,  $-C(R^2)_2-O-C(O)OR^y$ ,  $-C(R^2)_2OC(O)SR^y$ ,  $-alkyl-S-C(O)R^y$ ,  $-alkyl-S-S-alkylhydroxy$ , and  $-alkyl-S-S-S-alkylhydroxy$ ;

when  $Y$  is  $-NR^v$ , then  $R^{11}$  attached to  $-NR^v$  is selected from the group consisting of  $-H$ ,  $-[C(R^2)_2]_q-C(O)OR^y$ ,  $-C(R^2)_2C(O)OR^y$ ,  $-[C(R^2)_2]_q-C(O)SR^y$ , and  $-cycloalkylene-C(O)OR^y$ ;

$q$  is an integer 2 or 3;

Each  $R^z$  is selected from the group consisting of  $R^y$  and  $-H$ ;

Each  $R^y$  is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

Each  $R^x$  is independently selected from the group consisting of  $-H$ , and alkyl, or together  $R^x$  and  $R^x$  form a cycloalkyl group;

Each  $R^v$  is selected from the group consisting of  $-H$ , lower alkyl, acyloxyalkyl, alkoxy-carbonyloxyalkyl, and lower acyl;

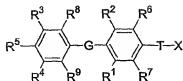
and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.



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19. The compound of claims 17 or 18 wherein  $R^7$  is selected from the group consisting of hydrogen, fluoro, chloro, amino, hydroxyl, and  $-O-CH_3$ .
20. The compound of claim 18 wherein G is  $-O-$ ; T is  $-CH_2CH(NH_2)-$ ;  $R^1$  and  $R^2$  are each iodo;  $R^4$  is selected from the group consisting of hydrogen and iodo;  $R^5$  is  $-OH$ ; and  $R^3$  is iodo.
21. The compound of claim 18 wherein G is  $-O-$ ; T is  $-N(H)C(O)-$ ;  $R^1$  and  $R^2$  are each methyl;  $R^4$  is hydrogen;  $R^5$  is  $-OH$ ; and  $R^3$  is  $-CH(OH)(4\text{-fluorophenyl})$ .
22. The compound of claim 18 wherein G is  $-CH_2-$ ; T is  $-OCH_2-$ ;  $R^1$  and  $R^2$  are each methyl;  $R^4$  is hydrogen;  $R^5$  is  $-OH$ ; and  $R^3$  is *iso*-propyl.
23. The compound of claim 18 wherein G is  $-O-$ ; T is  $-CH_2-$ ;  $R^1$  and  $R^2$  are each chloro;  $R^4$  is hydrogen;  $R^5$  is  $-OH$ ; and  $R^3$  is *iso*-propyl.
24. The compound of claim 18 wherein G is  $-O-$ ; T is  $-CH_2CH_2-$ ;  $R^1$  and  $R^2$  are each chloro;  $R^4$  is hydrogen;  $R^5$  is  $-OH$ ; and  $R^3$  is *iso*-propyl.
25. A compound of Formula VIII:

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wherein:

G is selected from the group consisting of -O-, -S-, -Se-, -S(=O)-, -S(=O)<sub>2</sub>-, -Se-, -CH<sub>2</sub>-, -CF<sub>2</sub>-, -CHF-, -C(O)-, -CH(OH)-, -CH(C<sub>1</sub>-C<sub>4</sub> alkyl)-, -CH(C<sub>1</sub>-C<sub>4</sub> alkoxy)-, -C(=CH<sub>2</sub>)-, -NH-, and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)-, or CH<sub>2</sub> linked to any of the preceding groups;

or G is R<sup>50</sup>-R<sup>51</sup> wherein;

R<sup>50</sup>-R<sup>51</sup> together are -C(R<sup>52</sup>)=C(R<sup>53</sup>)- or alternatively R<sup>50</sup> and R<sup>51</sup> are independently selected from O, S and -CH(R<sup>53</sup>)-, with the provisos that at least one R<sup>50</sup> and R<sup>51</sup> is -CH(R<sup>53</sup>)-, and when one of R<sup>50</sup> and R<sup>51</sup> is O or S, then R<sup>53</sup> is R<sup>54</sup>;

R<sup>54</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

R<sup>53</sup> is selected from hydrogen, halogen, hydroxyl, mercapto, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio; and

R<sup>52</sup> is selected from hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

T is selected from the group consisting of -(CR<sup>a</sup>)<sub>k</sub>-, -CR<sup>b</sup>=CR<sup>b</sup>-(CR<sup>a</sup>)<sub>n</sub>-, -(CR<sup>a</sup>)<sub>n</sub>-CR<sup>b</sup>=CR<sup>b</sup>-, -(CR<sup>a</sup>)<sub>2</sub>-CR<sup>b</sup>=CR<sup>b</sup>-(CR<sup>a</sup>)<sub>2</sub>-, -O(CR<sup>b</sup>)<sub>2</sub>(CR<sup>a</sup>)<sub>n</sub>-, -S(CR<sup>b</sup>)<sub>2</sub>(CR<sup>a</sup>)<sub>n</sub>-, -N(R<sup>c</sup>)(CR<sup>b</sup>)<sub>2</sub>(CR<sup>a</sup>)<sub>n</sub>-, -N(R<sup>b</sup>)C(O)(CR<sup>a</sup>)<sub>n</sub>-, -(CR<sup>a</sup>)<sub>m</sub>C(R<sup>b</sup>)(NR<sup>b</sup>)<sup>c</sup>-, -C(O)(CR<sup>a</sup>)<sub>m</sub>-, -(CR<sup>a</sup>)<sub>m</sub>C(O)-, -(CR<sup>a</sup>)<sub>2</sub>C(O)(CR<sup>a</sup>)<sub>n</sub>-, -(CR<sup>a</sup>)<sub>n</sub>C(O)(CR<sup>a</sup>)<sub>2</sub>-, -C(O)N(R<sup>b</sup>)(CR<sup>b</sup>)<sub>2</sub>(CR<sup>a</sup>)<sub>p</sub>-, -(CR<sup>b</sup>)<sub>2</sub>-O-(CR<sup>b</sup>)<sub>2</sub>-(CR<sup>a</sup>)<sub>p</sub>-, -(CR<sup>b</sup>)<sub>2</sub>-S-(CR<sup>b</sup>)<sub>2</sub>-(CR<sup>a</sup>)<sub>p</sub>-, -(CR<sup>b</sup>)<sub>2</sub>-N(R<sup>c</sup>)-(CR<sup>b</sup>)<sub>2</sub>-(CR<sup>a</sup>)<sub>p</sub>-, -(CR<sup>a</sup>)<sub>p</sub>-(CR<sup>b</sup>)<sub>2</sub>-O-(CR<sup>b</sup>)<sub>2</sub>-,

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$-(\text{CR}^a)_p-(\text{CR}^b)_2-\text{S}-(\text{CR}^b)_2-$ ,  $-(\text{CR}^a)_p-(\text{CR}^b)_2-\text{N}(\text{R}^c)-(\text{CR}^b)_2-$   
 and  $-(\text{CH}_2)_p\text{C}(\text{O})\text{N}(\text{R}^b)\text{C}(\text{R}^a)_2-$ ;

k is an integer from 0-4;

m is an integer from 0-3;

n is an integer from 0-2;

p is an integer from 0-1;

Each  $\text{R}^a$  is independently selected from the group consisting of hydrogen, optionally substituted  $-\text{C}_1\text{-C}_4$  alkyl, halogen,  $-\text{OH}$ , optionally substituted  $-\text{O}-\text{C}_1\text{-C}_4$  alkyl,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{F}$ , optionally substituted  $-\text{S}-\text{C}_1\text{-C}_4$  alkyl,  $-\text{NR}^b\text{R}^c$ , optionally substituted  $-\text{C}_2\text{-C}_4$  alkenyl, and optionally substituted  $-\text{C}_2\text{-C}_4$  alkynyl; with the proviso that when one  $\text{R}^a$  is attached to C through an O, S, or N atom, then the other  $\text{R}^a$  attached to the same C is a hydrogen, or attached via a carbon atom;

Each  $\text{R}^b$  is independently selected from the group consisting of hydrogen and optionally substituted  $-\text{C}_1\text{-C}_4$  alkyl;

Each  $\text{R}^c$  is independently selected from the group consisting of hydrogen and optionally substituted  $-\text{C}_1\text{-C}_4$  alkyl, optionally substituted  $-\text{C}(\text{O})-\text{C}_1\text{-C}_4$  alkyl, and  $-\text{C}(\text{O})\text{H}$ ;

$\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^6$ , and  $\text{R}^7$  are each independently selected from the group consisting of hydrogen, halogen, optionally substituted  $-\text{C}_1\text{-C}_4$  alkyl, optionally substituted  $-\text{S}-\text{C}_1\text{-C}_3$  alkyl, optionally substituted  $-\text{C}_2\text{-C}_4$  alkenyl, optionally substituted  $-\text{C}_2\text{-C}_4$  alkynyl,  $-\text{CF}_3$ ,  $-\text{CHF}_2$ ,  $-\text{CH}_2\text{F}$ ,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{F}$ , optionally substituted  $-\text{O}-\text{C}_1\text{-C}_3$  alkyl, and cyano; with the proviso that at least one of  $\text{R}^1$  and  $\text{R}^2$  is not hydrogen;

$\text{R}^8$  and  $\text{R}^9$  are each independently selected from the group consisting of hydrogen, halogen, optionally substituted  $-\text{C}_1\text{-C}_4$  alkyl, optionally substituted  $-\text{S}-\text{C}_1\text{-C}_3$  alkyl, optionally substituted  $-\text{C}_2\text{-C}_4$  alkenyl, optionally substituted  $-\text{C}_2\text{-C}_4$  alkynyl,  $-\text{CF}_3$ ,  $-\text{CHF}_2$ ,  $-\text{CH}_2\text{F}$ ,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{F}$ , optionally substituted  $-\text{O}-\text{C}_1\text{-C}_3$  alkyl, hydroxy,  $-(\text{CR}^a)_2\text{aryl}$ ,  $-(\text{CR}^a)_2\text{cycloalkyl}$ ,  $-(\text{CR}^a)_2\text{heterocycloalkyl}$ ,  $-\text{C}(\text{O})\text{aryl}$ ,  $-\text{C}(\text{O})\text{cycloalkyl}$ ,  $-\text{C}(\text{O})\text{heterocycloalkyl}$ ,  $-\text{C}(\text{O})\text{alkyl}$  and cyano; or

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$R^6$  and T are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations including 0 to 2 heteroatoms independently selected from  $-NR^i$ -,  $-O$ -, and  $-S$ -, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; and X is attached to this ring by a direct bond to a ring carbon, or by  $-(CR^a)_2$ - or  $-C(O)$ - bonded to a ring carbon or a ring nitrogen;

$R^i$  is selected from the group consisting of hydrogen,  $-C(O)C_1-C_4$  alkyl, and  $-C_1-C_4$  alkyl; or

$R^1$  and  $R^7$  are taken together along with the carbons to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^1$  and  $R^7$  are attached, including 0 to 2 heteroatoms independently selected from  $-NR^h$ -,  $-O$ -, and  $-S$ -, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

$R^3$  and  $R^4$  are each independently selected from the group consisting of hydrogen, halogen,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , cyano, optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^a)_m$ aryl, optionally substituted  $-(CR^a)_m$ cycloalkyl, optionally substituted  $-(CR^a)_m$ heterocycloalkyl,  $-C(R^b)=C(R^b)$ -aryl,  $-C(R^b)=C(R^b)$ -cycloalkyl,  $-C(R^b)=C(R^b)$ -heterocycloalkyl,  $-C\equiv C$ (aryl),  $-C\equiv C$ (cycloalkyl),  $-C\equiv C$ (heterocycloalkyl),  $-(CR^a)_n(CR^b)_2NR^fR^g$ ,  $-OR^d$ ,  $-SR^d$ ,  $-S(=O)R^e$ ,  $-S(=O)_2R^e$ ,  $-S(=O)_2NR^fR^g$ ,  $-C(O)NR^fR^g$ ,  $-C(O)OR^h$ ,  $-C(O)R^e$ ,  $-N(R^b)C(O)R^e$ ,  $-N(R^b)C(O)NR^fR^g$ ,  $-N(R^b)S(=O)_2R^e$ ,  $-N(R^b)S(=O)_2NR^fR^g$ , and  $-NR^fR^g$ ;

Each  $R^d$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally

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substituted  $-(CR^b)_n$ cycloalkyl, optionally substituted  $-(CR^b)_n$ heterocycloalkyl, and  $-C(O)NR^fR^g$ ;

Each  $R^e$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, and optionally substituted  $-(CR^b)_n$ heterocycloalkyl;

$R^f$  and  $R^g$  are each independently selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, and optionally substituted  $-(CR^b)_n$ heterocycloalkyl, or  $R^f$  and  $R^g$  may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4 unsaturations, said heterocyclic ring may contain a second heterogroup within the ring selected from the group consisting of O,  $NR^c$ , and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally substituted  $-C_1-C_4$  alkyl,  $-OR^b$ , oxo, cyano,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ , optionally substituted phenyl, and  $-C(O)OR^b$ ;

Each  $R^h$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, and optionally substituted  $-(CR^b)_n$ heterocycloalkyl; or

$R^3$  and  $R^8$  are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^3$  and  $R^8$  are attached, including 0 to 2 heteroatoms independently selected from  $-NR^h$ ,  $-O$ , and  $-S$ -, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; or

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$R^8$  and G are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring comprising  $-\text{CH}=\text{CH}-\text{CH}=\text{}$ ,  $-\text{N}=\text{CH}-\text{CH}=\text{}$ ,  $-\text{CH}=\text{N}-\text{CH}=\text{}$  or  $-\text{CH}=\text{CH}-\text{N}=\text{}$ ;

$R^5$  is selected from the group consisting of  $-\text{OH}$ , optionally substituted  $-\text{OC}_1-\text{C}_6$  alkyl,  $-\text{OC}(\text{O})\text{R}^e$ ,  $-\text{OC}(\text{O})\text{OR}^h$ ,  $-\text{NHC}(\text{O})\text{OR}^h$ ,  $-\text{OC}(\text{O})\text{NH}(\text{R}^h)$ ,  $-\text{F}$ ,  $-\text{NHC}(\text{O})\text{R}^e$ ,  $-\text{NHS}(=\text{O})\text{R}^e$ ,  $-\text{NHS}(=\text{O})\text{R}^e$ ,  $-\text{NHC}(=\text{S})\text{NH}(\text{R}^h)$ , and  $-\text{NHC}(\text{O})\text{NH}(\text{R}^h)$ ; or

$R^3$  and  $R^5$  are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^3$  and  $R^5$  are attached, including 0 to 2 heteroatoms independently selected from  $-\text{NR}^h$ ,  $-\text{O}-$ , and  $-\text{S}-$ , with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

X is  $\text{P}(\text{O})(\text{YR}^{11})\text{Y}''$ ;

$\text{Y}''$  is selected from the group consisting of hydrogen, optionally substituted  $-\text{C}_1-\text{C}_6$ -alkyl,  $-\text{CF}_3$ ,  $-\text{CHF}_2$ ,  $-\text{CH}_2\text{F}$ ,  $-\text{CH}_2\text{OH}$ , optionally substituted  $-\text{C}_2-\text{C}_6$  alkenyl, optionally substituted  $-\text{C}_2-\text{C}_6$  alkynyl, optionally substituted  $-(\text{CR}^a)_n$  cycloalkyl, optionally substituted  $(\text{CR}^a)_n$  heterocycloalkyl,  $-(\text{CR}^a)_k\text{S}(=\text{O})\text{R}^e$ ,  $-(\text{CR}^a)_k\text{S}(=\text{O})_2\text{R}^e$ ,  $-(\text{CR}^a)_k\text{S}(=\text{O})_2\text{NR}^f\text{R}^g$ ,  $-(\text{CR}^a)_k\text{C}(\text{O})\text{NR}^f\text{R}^g$ , and  $-(\text{CR}^a)_k\text{C}(\text{O})\text{R}^e$ ;

Y is selected from the group consisting of  $-\text{O}-$ , and  $-\text{NR}^v$ ;

when Y is  $-\text{O}-$ ,  $\text{R}^{11}$  attached to  $-\text{O}-$  is selected from the group consisting of higher alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted  $\text{CH}_2$ -heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted  $-\text{alkylaryl}$ ,  $-\text{C}(\text{R}^2)_2\text{OC}(\text{O})\text{NR}^2$ ,  $-\text{NR}^2-\text{C}(\text{O})-\text{R}^2$ ,  $-\text{C}(\text{R}^2)_2-\text{OC}(\text{O})\text{R}^2$ ,  $-\text{C}(\text{R}^2)_2-\text{O}-\text{C}(\text{O})\text{OR}^2$ ,  $-\text{C}(\text{R}^2)_2\text{OC}(\text{O})\text{SR}^2$ ,  $-\text{alkyl-S-C}(\text{O})\text{R}^2$ ,  $-\text{alkyl-S-S-alkylhydroxy}$ , and  $-\text{alkyl-S-S-S-alkylhydroxy}$ ;

when Y is  $-\text{NR}^v$ , then  $\text{R}^{11}$  attached to  $-\text{NR}^v$  is selected from the group consisting of  $-\text{H}$ ,  $-\text{C}(\text{R}^2)_4-\text{C}(\text{O})\text{R}^2$ ,  $-\text{C}(\text{R}^2)_2\text{C}(\text{O})\text{OR}^2$ ,  $-\text{C}(\text{R}^2)_2-\text{C}(\text{O})\text{SR}^2$ , and  $-\text{cycloalkylene-C}(\text{O})\text{OR}^2$ ;

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q is an integer 2 or 3;

Each  $R^z$  is selected from the group consisting of  $R^y$  and -H;

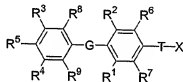
Each  $R^y$  is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

Each  $R^x$  is independently selected from the group consisting of -H, and alkyl, or together  $R^x$  and  $R^x$  form a cycloalkyl group;

Each  $R^v$  is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

26. A compound of Formula VIII:



wherein:

G is selected from the group consisting of -O-, -S-, -Se-, -S(=O)-, -S(=O)<sub>2</sub>-, -Se-, -CH<sub>2</sub>-, -CF<sub>2</sub>-, -CHF-, -C(O)-, -CH(OH)-, -CH(C<sub>1</sub>-C<sub>4</sub> alkyl)-, -CH(C<sub>1</sub>-C<sub>4</sub> alkoxy)-, -C(=CH<sub>2</sub>)-, -NH-, and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)-, or CH<sub>2</sub> linked to any of the preceding groups;

or G is R<sup>50</sup>-R<sup>51</sup> wherein;

R<sup>50</sup>-R<sup>51</sup> together are -C(R<sup>52</sup>)=C(R<sup>52</sup>)- or alternatively R<sup>50</sup> and R<sup>51</sup> are independently selected from O, S and -CH(R<sup>53</sup>)-, with the provisos that at least one R<sup>50</sup> and R<sup>51</sup> is -CH(R<sup>53</sup>)-, and when one of R<sup>50</sup> and R<sup>51</sup> is O or S, then R<sup>53</sup> is R<sup>54</sup>;

R<sup>54</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

R<sup>53</sup> is selected from hydrogen, halogen, hydroxyl, mercapto, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy,

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trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio; and

$S^{52}$  is selected from hydrogen, halogen,  $C_1$ - $C_4$  alkyl,  $C_2$ - $C_4$  alkenyl,  $C_2$ - $C_4$  alkynyl,  $C_1$ - $C_4$  alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

T is selected from the group consisting of  $-(CR^a)_k$ ,  $-CR^b=CR^b-(CR^a)_n$ ,  $-(CR^a)_n-CR^b=CR^b$ ,  $-(CR^a)_2-CR^b=CR^b-(CR^a)_2$ ,  $-O(CR^b)(CR^a)_n$ ,  $-S(CR^b)(CR^a)_n$ ,  $-N(R^b)(CR^b)(CR^a)_n$ ,  $-N(R^b)C(O)(CR^a)_n$ ,  $-(CR^a)_mC(R^b)(NR^bR^c)$ ,  $-C(O)(CR^a)_m$ ,  $-(CR^a)_mC(O)-$ ,  $-(CR^b)_2-O-(CR^b)_2-(CR^a)_p$ ,  $-(CR^b)_2-S-(CR^b)_2-(CR^a)_p$ ,  $-(CR^b)_2-N(R^b)-$ ,  $(CR^b)_2-(CR^b)_2$ ,  $-(CR^b)_p-(CR^b)_2-O-(CR^b)_2$ ,  $-(CR^b)_p$ ,  $(CR^b)_2-S-(CR^b)_2$ ,  $-(CR^a)_p-(CR^b)_2-N(R^b)-(CR^b)_2$  and  $-(CR^b)_2-O-(CR^a)_2$ .

k is an integer from 0-4;

m is an integer from 0-3;

n is an integer from 0-2;

p is an integer from 0-1;

Each  $R^a$  is independently selected from the group consisting of hydrogen, optionally substituted  $-C_1$ - $C_4$  alkyl, halogen,  $-OH$ , optionally substituted  $-O-C_1$ - $C_4$  alkyl,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-S-C_1$ - $C_4$  alkyl,  $-NR^bR^c$ , optionally substituted  $-C_2$ - $C_4$  alkenyl, and optionally substituted  $-C_2$ - $C_4$  alkynyl; with the proviso that when one  $R^a$  is attached to C through an O, S, or N atom, then the other  $R^a$  attached to the same C is a hydrogen, or attached via a carbon atom;

Each  $R^b$  is independently selected from the group consisting of hydrogen and optionally substituted  $-C_1$ - $C_4$  alkyl;

Each  $R^c$  is independently selected from the group consisting of hydrogen and optionally substituted  $-C_1$ - $C_4$  alkyl, optionally substituted  $-C(O)-C_1$ - $C_4$  alkyl, and  $-C(O)H$ ;

$R^1$ ,  $R^2$ ,  $R^6$ , and  $R^7$  are each independently selected from the group consisting of hydrogen, halogen, optionally substituted  $-C_1$ - $C_4$  alkyl, optionally



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substituted -S-C<sub>1</sub>-C<sub>3</sub> alkyl, optionally substituted -C<sub>2</sub>-C<sub>4</sub> alkenyl, optionally substituted -C<sub>2</sub>-C<sub>4</sub> alkynyl, -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>F, optionally substituted -O-C<sub>1</sub>-C<sub>3</sub> alkyl, and cyano; with the proviso that at least one of R<sup>1</sup> and R<sup>2</sup> is not hydrogen;

R<sup>8</sup> and R<sup>9</sup> are each independently selected from the group consisting of hydrogen, halogen, optionally substituted -C<sub>1</sub>-C<sub>4</sub> alkyl, optionally substituted -S-C<sub>1</sub>-C<sub>3</sub> alkyl, optionally substituted -C<sub>2</sub>-C<sub>4</sub> alkenyl, optionally substituted -C<sub>2</sub>-C<sub>4</sub> alkynyl, -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>F, optionally substituted -O-C<sub>1</sub>-C<sub>3</sub> alkyl, hydroxy, -(CR<sup>a</sup>)<sub>2</sub>aryl, -(CR<sup>a</sup>)<sub>2</sub>cycloalkyl, -(CR<sup>a</sup>)<sub>2</sub>heterocycloalkyl, -C(O)aryl, -C(O)cycloalkyl, -C(O)heterocycloalkyl, -C(O)alkyl and cyano; or

R<sup>6</sup> and T are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations including 0 to 2 heteroatoms independently selected from -NR<sup>1</sup>-, -O-, and -S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; and X is attached to this ring by a direct bond to a ring carbon, or by -(CR<sup>a</sup>)<sub>2</sub>- or -C(O)- bonded to a ring carbon or a ring nitrogen;

R<sup>1</sup> is selected from the group consisting of hydrogen, -C(O)C<sub>1</sub>-C<sub>4</sub> alkyl, and -C<sub>1</sub>-C<sub>4</sub> alkyl; or

R<sup>1</sup> and R<sup>7</sup> are taken together along with the carbons to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which R<sup>1</sup> and R<sup>7</sup> are attached, including 0 to 2 heteroatoms independently selected from -NR<sup>b</sup>-, -O-, and -S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of hydrogen, halogen, -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>F, cyano, optionally substituted -C<sub>1</sub>-C<sub>12</sub> alkyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkenyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkynyl, optionally substituted -(CR<sup>a</sup>)<sub>m</sub>aryl,

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optionally substituted  $-(CR^a)_m$ cycloalkyl, optionally substituted  $-(CR^a)_m$ heterocycloalkyl,  $-C(R^b)=C(R^b)$ -aryl,  $-C(R^b)=C(R^b)$ -cycloalkyl,  $-C(R^b)=C(R^b)$ -heterocycloalkyl,  $-C\equiv C(aryl)$ ,  $-C\equiv C(cycloalkyl)$ ,  $-C\equiv C(heterocycloalkyl)$ ,  $-(CR^a)_h(CR^b)_2NR^fR^g$ ,  $-OR^d$ ,  $-SR^d$ ,  $-S(=O)R^e$ ,  $-S(=O)_2R^e$ ,  $-S(=O)_2NR^fR^g$ ,  $-C(O)NR^fR^g$ ,  $-C(O)OR^h$ ,  $-C(O)R^e$ ,  $-N(R^b)C(O)R^e$ ,  $-N(R^b)C(O)NR^fR^g$ ,  $-N(R^b)S(=O)_2R^e$ ,  $-N(R^b)S(=O)_2NR^fR^g$ , and  $-NR^fR^g$ ;

Each  $R^d$  is selected from the group consisting of optionally substituted  $-C_1$ - $C_{12}$  alkyl, optionally substituted  $-C_2$ - $C_{12}$  alkenyl, optionally substituted  $-C_2$ - $C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, optionally substituted  $-(CR^b)_n$ heterocycloalkyl, and  $-C(O)NR^fR^g$ ;

Each  $R^e$  is selected from the group consisting of optionally substituted  $-C_1$ - $C_{12}$  alkyl, optionally substituted  $-C_2$ - $C_{12}$  alkenyl, optionally substituted  $-C_2$ - $C_{12}$  alkynyl, optionally substituted  $-(CR^a)_n$ aryl, optionally substituted  $-(CR^a)_n$ cycloalkyl, and optionally substituted  $-(CR^a)_n$ heterocycloalkyl;

$R^f$  and  $R^g$  are each independently selected from the group consisting of hydrogen, optionally substituted  $-C_1$ - $C_{12}$  alkyl, optionally substituted  $-C_2$ - $C_{12}$  alkenyl, optionally substituted  $-C_2$ - $C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, and optionally substituted  $-(CR^b)_n$ heterocycloalkyl, or  $R^f$  and  $R^g$  may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4 unsaturations, said heterocyclic ring may contain a second heterogroup within the ring selected from the group consisting of O,  $NR^e$ , and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally substituted  $-C_1$ - $C_4$  alkyl,  $-OR^b$ , oxo, cyano,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ , optionally substituted phenyl, and  $-C(O)OR^h$ ;

Each  $R^h$  is selected from the group consisting of optionally substituted  $-C_1$ - $C_{12}$  alkyl, optionally substituted  $-C_2$ - $C_{12}$  alkenyl, optionally substituted  $-C_2$ - $C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally

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substituted  $-(CR^b)_n$ cycloalkyl, and optionally substituted  $-(CR^b)_n$ heterocycloalkyl; or

$R^3$  and  $R^8$  are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^3$  and  $R^8$  are attached, including 0 to 2 heteroatoms independently selected from  $-NR^h$ , -O-, and -S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; or

$R^8$  and G are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring comprising  $-CH=CH-CH=$ ,  $-N=CH-CH=$ ,  $-CH=N-CH=$  or  $-CH=CH-N=$ ;

$R^5$  is selected from the group consisting of -OH, optionally substituted  $-OC_1-C_6$  alkyl,  $-OC(O)R^e$ ,  $-OC(O)OR^h$ ,  $-NHC(O)OR^h$ ,  $-OC(O)NH(R^h)$ , -F,  $-NHC(O)R^e$ ,  $-NHS(=O)R^e$ ,  $-NHS(=O)_2R^e$ ,  $-NHC(=S)NH(R^h)$ , and  $-NHC(O)NH(R^h)$ ; or

$R^3$  and  $R^5$  are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^3$  and  $R^5$  are attached, including 0 to 2 heteroatoms independently selected from  $-NR^h$ , -O-, and -S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

X is  $P(O)(YR^{11})Y''$ ;

$Y''$  is selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_6$ -alkyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-CH_2OH$ , optionally substituted  $-C_2-C_6$  alkenyl, optionally substituted  $-C_2-C_6$  alkynyl, optionally substituted  $-(CR^a)_n$ cycloalkyl, optionally substituted  $(CR^a)_n$ heterocycloalkyl,  $-(CR^a)_kS(=O)R^e$ ,  $-(CR^a)_kS(=O)_2R^e$ ,  $-(CR^a)_kS(=O)_2NR^fR^g$ ,  $-(CR^a)_kC(O)NR^fR^g$ , and  $-(CR^a)_kC(O)R^e$ ;

Y is selected from the group consisting of -O-, and  $-NR^v$ ;

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when Y is -O-, R<sup>11</sup> attached to -O- is selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH<sub>2</sub>-heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, -C(R<sup>2</sup>)<sub>2</sub>OC(O)NR<sup>2</sup><sub>2</sub>, -NR<sup>2</sup>-C(O)-R<sup>2</sup>, -C(R<sup>2</sup>)<sub>2</sub>-OC(O)R<sup>2</sup>, -C(R<sup>2</sup>)<sub>2</sub>-O-C(O)OR<sup>2</sup>, -C(R<sup>2</sup>)<sub>2</sub>OC(O)SR<sup>2</sup>, -alkyl-S-C(O)R<sup>2</sup>, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is -NR<sup>v</sup>-, then R<sup>11</sup> attached to -NR<sup>v</sup>- is selected from the group consisting of -H, -[C(R<sup>2</sup>)<sub>2</sub>]<sub>q</sub>-C(O)OR<sup>2</sup>, -C(R<sup>2</sup>)<sub>2</sub>C(O)OR<sup>2</sup>, -[C(R<sup>2</sup>)<sub>2</sub>]<sub>q</sub>-C(O)SR<sup>2</sup>, and -cycloalkylene-C(O)OR<sup>2</sup>;

q is an integer 2 or 3;

Each R<sup>2</sup> is selected from the group consisting of R<sup>2</sup> and -H;

Each R<sup>2</sup> is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

Each R<sup>x</sup> is independently selected from the group consisting of -H, and alkyl, or together R<sup>x</sup> and R<sup>x</sup> form a cycloalkyl group;

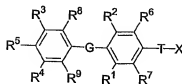
Each R<sup>v</sup> is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

with the proviso that:

a) when G is -O-, T is -CH<sub>2</sub>-, R<sup>1</sup> and R<sup>2</sup> are each chloro, R<sup>3</sup> is phenyl, R<sup>4</sup> is hydrogen, and R<sup>5</sup> is -OH, then X is not P(O)(OH)CH<sub>3</sub> or P(O)(OCH<sub>2</sub>CH<sub>3</sub>)CH<sub>3</sub>;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

27. A compound of Formula VIII:



wherein:

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G is selected from the group consisting of -O-, -S-, -Se-, -S(=O)-, -S(=O)<sub>2</sub>-, -Se-, -CH<sub>2</sub>-, -CF<sub>2</sub>-, -CHF-, -C(O)-, -CH(OH)-, -CH(C<sub>1</sub>-C<sub>4</sub> alkyl)-, -CH(C<sub>1</sub>-C<sub>4</sub> alkoxy)-, -C(=CH<sub>2</sub>)-, -NH-, and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)-, or CH<sub>2</sub> linked to any of the preceding groups;

or G is R<sup>50</sup>-R<sup>51</sup> wherein;

R<sup>50</sup>-R<sup>51</sup> together are -C(R<sup>52</sup>)=C(R<sup>53</sup>)- or alternatively R<sup>50</sup> and R<sup>51</sup> are independently selected from O, S and -CH(R<sup>53</sup>)-, with the provisos that at least one R<sup>50</sup> and R<sup>51</sup> is -CH(R<sup>53</sup>)-, and when one of R<sup>50</sup> and R<sup>51</sup> is O or S, then R<sup>53</sup> is R<sup>54</sup>;

R<sup>54</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

R<sup>53</sup> is selected from hydrogen, halogen, hydroxyl, mercapto, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio; and

R<sup>52</sup> is selected from hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

T is selected from the group consisting of -(CR<sup>a</sup>)<sub>k</sub>-, -CR<sup>b</sup>=CR<sup>b</sup>-(CR<sup>a</sup>)<sub>n</sub>-, -(CR<sup>a</sup>)<sub>n</sub>-CR<sup>b</sup>=CR<sup>b</sup>-, -(CR<sup>a</sup>)<sub>2</sub>-CR<sup>b</sup>=CR<sup>b</sup>-(CR<sup>a</sup>)<sub>2</sub>-, -O(CR<sup>b</sup>)<sub>2</sub>(CR<sup>a</sup>)<sub>n</sub>-, -S(CR<sup>b</sup>)<sub>2</sub>(CR<sup>a</sup>)<sub>n</sub>-, -N(R<sup>c</sup>)(CR<sup>b</sup>)<sub>2</sub>(CR<sup>a</sup>)<sub>n</sub>-, -N(R<sup>b</sup>)C(O)(CR<sup>a</sup>)<sub>n</sub>-, -(CR<sup>a</sup>)<sub>n</sub>C(R<sup>b</sup>)(NR<sup>b</sup>R<sup>c</sup>)-, -C(O)(CR<sup>a</sup>)<sub>m</sub>-, -(CR<sup>a</sup>)<sub>m</sub>C(O)-, -(CR<sup>b</sup>)<sub>2</sub>-O-(CR<sup>b</sup>)<sub>2</sub>-(CR<sup>a</sup>)<sub>p</sub>-, -(CR<sup>b</sup>)<sub>2</sub>-S-(CR<sup>b</sup>)<sub>2</sub>-(CR<sup>a</sup>)<sub>p</sub>-, -(CR<sup>b</sup>)<sub>2</sub>-N(R<sup>c</sup>)-(CR<sup>b</sup>)<sub>2</sub>-(CR<sup>a</sup>)<sub>p</sub>-, -(CR<sup>a</sup>)<sub>p</sub>-(CR<sup>b</sup>)<sub>2</sub>-O-(CR<sup>b</sup>)<sub>2</sub>-, -(CR<sup>a</sup>)<sub>2</sub>-(CR<sup>b</sup>)<sub>2</sub>-S-(CR<sup>b</sup>)<sub>2</sub>-, -(CR<sup>a</sup>)<sub>p</sub>-(CR<sup>b</sup>)<sub>2</sub>-N(R<sup>c</sup>)-(CR<sup>b</sup>)<sub>2</sub>- and -(CR<sup>a</sup>)<sub>1,2</sub>-O-(CR<sup>a</sup>)<sub>1,2</sub>-;

k is an integer from 0-4;

m is an integer from 0-3;

n is an integer from 0-2;

p is an integer from 0-1;

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Each  $R^a$  is independently selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_4$  alkyl, halogen,  $-OH$ , optionally substituted  $-O-C_1-C_4$  alkyl,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-S-C_1-C_4$  alkyl,  $-NR^bR^c$ , optionally substituted  $-C_2-C_4$  alkenyl, and optionally substituted  $-C_2-C_4$  alkynyl; with the proviso that when one  $R^a$  is attached to C through an O, S, or N atom, then the other  $R^a$  attached to the same C is a hydrogen, or attached via a carbon atom;

Each  $R^b$  is independently selected from the group consisting of hydrogen and optionally substituted  $-C_1-C_4$  alkyl;

Each  $R^c$  is independently selected from the group consisting of hydrogen and optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-C(O)-C_1-C_4$  alkyl, and  $-C(O)H$ ;

$R^1$ ,  $R^2$ ,  $R^6$ , and  $R^7$  are each independently selected from the group consisting of hydrogen, halogen, optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-S-C_1-C_3$  alkyl, optionally substituted  $-C_2-C_4$  alkenyl, optionally substituted  $-C_2-C_4$  alkynyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-O-C_1-C_3$  alkyl, and cyano; with the proviso that at least one of  $R^1$  and  $R^2$  is not hydrogen;

$R^8$  and  $R^9$  are each independently selected from the group consisting of hydrogen, halogen, optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-S-C_1-C_3$  alkyl, optionally substituted  $-C_2-C_4$  alkenyl, optionally substituted  $-C_2-C_4$  alkynyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-O-C_1-C_3$  alkyl, hydroxy,  $-(CR^a)_2$ aryl,  $-(CR^a)_2$ cycloalkyl,  $-(CR^a)_2$ heterocycloalkyl,  $-C(O)aryl$ ,  $-C(O)cycloalkyl$ ,  $-C(O)heterocycloalkyl$ ,  $-C(O)alkyl$  and cyano; or

$R^6$  and T are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations including 0 to 2 heteroatoms independently selected from  $-NR^i$ -,  $-O$ -, and  $-S$ -, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; and X is attached to this ring by a direct

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bond to a ring carbon, or by  $-(CR^a_2)-$  or  $-C(O)-$  bonded to a ring carbon or a ring nitrogen;

$R^i$  is selected from the group consisting of hydrogen,  $-C(O)C_1-C_4$  alkyl, and  $-C_1-C_4$  alkyl; or

$R^1$  and  $R^7$  are taken together along with the carbons to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^1$  and  $R^7$  are attached, including 0 to 2 heteroatoms independently selected from  $-NR^h$ ,  $-O-$ , and  $-S-$ , with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

$R^3$  and  $R^4$  are each independently selected from the group consisting of hydrogen, halogen,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , cyano, optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^a_2)_m$ aryl, optionally substituted  $-(CR^a_2)_m$ cycloalkyl, optionally substituted  $-(CR^b)_m$ heterocycloalkyl,  $-C(R^b)=C(R^b)$ -aryl,  $-C(R^b)=C(R^b)$ -cycloalkyl,  $-C(R^b)=C(R^b)$ -heterocycloalkyl,  $-C\equiv C$ (aryl),  $-C\equiv C$ (cycloalkyl),  $-C\equiv C$ (heterocycloalkyl),  $-(CR^a_2)_m(CR^b_2)NR^fR^g$ ,  $-OR^d$ ,  $-SR^d$ ,  $-S(=O)R^e$ ,  $-S(=O)_2R^e$ ,  $-S(=O)_2NR^fR^g$ ,  $-C(O)NR^fR^g$ ,  $-C(O)OR^h$ ,  $-C(O)R^e$ ,  $-N(R^b)C(O)R^e$ ,  $-N(R^b)C(O)NR^fR^g$ ,  $-N(R^b)S(=O)_2R^e$ ,  $-N(R^b)S(=O)_2NR^fR^g$ , and  $-NR^fR^g$ ;

Each  $R^d$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b_2)_n$ aryl, optionally substituted  $-(CR^b_2)_n$ cycloalkyl, optionally substituted  $-(CR^b_2)_n$ heterocycloalkyl, and  $-C(O)NR^fR^g$ ;

Each  $R^e$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^a_2)_n$ aryl, optionally substituted  $-(CR^a_2)_n$ cycloalkyl, and optionally substituted  $-(CR^a_2)_n$ heterocycloalkyl;

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$R^f$  and  $R^g$  are each independently selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, and optionally substituted  $-(CR^b)_n$ heterocycloalkyl, or  $R^f$  and  $R^g$  may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4 unsaturations, said heterocyclic ring may contain a second heterogroup within the ring selected from the group consisting of O,  $NR^c$ , and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally substituted  $-C_1-C_4$  alkyl,  $-OR^b$ , oxo, cyano,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ , optionally substituted phenyl, and  $-C(O)OR^h$ ;

Each  $R^h$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, and optionally substituted  $-(CR^b)_n$ heterocycloalkyl; or

$R^3$  and  $R^8$  are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^3$  and  $R^8$  are attached, including 0 to 2 heteroatoms independently selected from  $-NR^b$ ,  $-O-$ , and  $-S-$ , with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; or

$R^8$  and G are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring comprising  $-CH=CH-CH=$ ,  $-N=CH-CH=$ ,  $-CH=N-CH=$  or  $-CH=CH-N=$ ;

$R^5$  is selected from the group consisting of  $-OH$ , optionally substituted  $-OC_1-C_6$  alkyl,  $-OC(O)R^e$ ,  $-OC(O)OR^h$ ,  $-NHC(O)OR^h$ ,  $-OC(O)NH(R^b)$ ,  $-F$ ,  $-NHC(O)R^e$ ,  $-NHS(=O)R^e$ ,  $-NHS(=O)_2R^e$ ,  $-NHC(=S)NH(R^b)$ , and  $-NHC(O)NH(R^b)$ ; or



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$R^3$  and  $R^5$  are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^3$  and  $R^5$  are attached, including 0 to 2 heteroatoms independently selected from  $-NR^h$ -,  $-O$ -, and  $-S$ -, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

X is  $P(O)(YR^{11})Y''$ ;

$Y''$  is selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_6$ -alkyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-CH_2OH$ , optionally substituted  $-C_2-C_6$  alkenyl, optionally substituted  $-C_2-C_6$  alkynyl, optionally substituted  $-(CR^a)_n$ cycloalkyl, optionally substituted  $(CR^a)_n$ heterocycloalkyl,  $-(CR^a)_kS(=O)R^e$ ,  $-(CR^a)_kS(=O)_2R^e$ ,  $-(CR^a)_kS(=O)_2NR^fR^g$ ,  $-(CR^a)_kC(O)NR^fR^g$ , and  $-(CR^a)_kC(O)R^e$ ;

Y is selected from the group consisting of  $-O$ -, and  $-NR^y$ ;

when Y is  $-O$ -,  $R^{11}$  attached to  $-O$ - is selected from the group consisting of  $-H$ , alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted  $CH_2$ -heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted  $-alkylaryl$ ,  $-C(R^2)_2OC(O)NR^2$ ,  $-NR^2-C(O)-R^y$ ,  $-C(R^2)_2-OC(O)R^y$ ,  $-C(R^2)_2-O-C(O)OR^y$ ,  $-C(R^2)_2OC(O)SR^y$ ,  $-alkyl-S-C(O)R^y$ ,  $-alkyl-S-S-alkylhydroxy$ , and  $-alkyl-S-S-S-alkylhydroxy$ ;

when Y is  $-NR^y$ -, then  $R^{11}$  attached to  $-NR^y$ - is selected from the group consisting of  $-H$ ,  $-[C(R^2)_2]_q-C(O)OR^y$ ,  $-C(R^2)_2C(O)OR^y$ ,  $-[C(R^2)_2]_q-C(O)SR^y$ , and  $-cycloalkylene-C(O)OR^y$ ;

q is an integer 2 or 3;

Each  $R^2$  is selected from the group consisting of  $R^y$  and  $-H$ ;

Each  $R^y$  is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;


Each  $R^x$  is independently selected from the group consisting of  $-H$ , and alkyl, or together  $R^x$  and  $R^x$  form a cyclic alkyl group;

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Each  $R^v$  is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

with the proviso that:

a) when G is -O-, -S-, -Se-, -S(=O)-, -S(=O)<sub>2</sub>-, -CH<sub>2</sub>-, -C(O)-, -NH- and, T is -(CH<sub>2</sub>)<sub>0-4</sub>- or -C(O)NH(CR<sup>b</sup>)<sub>2</sub>-,  $R^1$  and  $R^2$  are independently chosen from the group consisting of hydrogen, halogen, -C<sub>1</sub>-C<sub>4</sub> alkyl,  $R^8$  and  $R^9$  are each independently selected from hydrogen, halogen and C<sub>1-4</sub>alkyl,  $R^6$  and  $R^7$  are each independently selected from hydrogen, halogen O-C<sub>1-3</sub>alkyl, hydroxy, cyano and C<sub>1-4</sub>alkyl,  $R^3$  is -C(O)NR<sup>25</sup>R<sup>26</sup>, -CH<sub>2</sub>-

NR<sup>25</sup>R<sup>26</sup>, -NR<sup>25</sup>-C(O)R<sup>26</sup>, -OR<sup>27</sup>, R<sup>28</sup>, or ,  $R^4$  is hydrogen, halogen, cyano or alkyl, and  $R^5$  is -OH,  $R^{25}$  and  $R^{26}$  are each independently selected from the group consisting of hydrogen, aryl, heteroaryl, alkyl, cycloalkyl, aralkyl or heteroaralkyl,  $R^{27}$  is aryl, heteroaryl, alkyl, aralkyl, or heteroaralkyl,  $R^{28}$  is aryl, heteroaryl, or cycloalkyl,  $R^{29}$  is hydrogen, aryl, heteroaryl, alkyl, aralkyl, heteroaralkyl, then X is not -P(O)(OH)C<sub>1</sub>-C<sub>6</sub> alkyl or -P(O)(O-lower alkyl)C<sub>1</sub>-C<sub>6</sub> alkyl;

b) when G is -O-, -S-, -Se-, -S(=O)-, -S(=O)<sub>2</sub>-, -CH<sub>2</sub>-, -CF<sub>2</sub>-, -C(O)-, -NH- and, T is -C(O)NH(CR<sup>b</sup>)<sub>2</sub>-,  $R^1$  and  $R^2$  are independently halogen, cyano, -C<sub>1</sub>-C<sub>4</sub> alkyl,  $R^8$  and  $R^9$  are each independently selected from hydrogen, halogen and C<sub>1-4</sub>alkyl,  $R^6$  and  $R^7$  are each independently selected from hydrogen, halogen O-C<sub>1-3</sub>alkyl, hydroxy, cyano and C<sub>1-4</sub>alkyl,  $R^3$  is halogen, -C<sub>1</sub>-C<sub>6</sub> alkyl, -C<sub>2</sub>-C<sub>6</sub> alkynyl, -C<sub>4</sub>-C<sub>7</sub> cycloalkenyl, -C<sub>3</sub>-C<sub>7</sub> cycloalkoxy, -S(=O)<sub>2</sub>(NR<sup>14</sup>R<sup>15</sup>), -N(R<sup>16</sup>)S(=O)<sub>2</sub>R<sup>17</sup>, -SR<sup>17</sup>, -S(=O)R<sup>17</sup>, -S(=O)<sub>2</sub>R<sup>17</sup>, -C(O)R<sup>16</sup>, or -CR<sup>18</sup>(OR<sup>16</sup>)R<sup>19</sup>,  $R^4$  is halogen, cyano or alkyl, and  $R^5$  is -OH, optionally substituted -OC<sub>1</sub>-C<sub>6</sub> alkyl, aroyl or alkanoyl,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$ ,  $R^{18}$  and  $R^{19}$  are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroalkyl, arylalkyl, and heteroarylalkyl, or  $R^{14}$  and  $R^{15}$  may be joined so as to comprise a chain of 3 to 6 methylene groups to form a ring of 4 to 7-membered in size,  $R^{17}$  is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroalkyl, arylalkyl, and

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heteroarylalkyl, then X is not  $-P(O)(OH)C_1-C_6$  alkyl or  $-P(O)(O-lower\ alkyl)C_1-C_6$  alkyl;

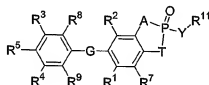
and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

28. The compound of any one of claims 1-3, 17, 18, or 25-27 wherein T is selected from the group consisting of  $-(CR^a_2)_n-$ ,  $-O(CR^b_2)(CR^a_2)_p-$ ,  $-N(R^c)(CR^b_2)(CR^a_2)_p-$ ,  $-S(CR^b_2)(CR^a_2)_p-$ ,  $-N(R^c)C(O)-$ , and  $-CH_2CH(NR^eR^b)-$ .
29. The compound of claim 28 wherein T is  $-(CR^a_2)_n-$ ,  $-O(CR^b_2)(CR^a_2)_p-$  or  $-N(R^c)(CR^b_2)(CR^a_2)_p-$ .
30. The compound of claim 27 wherein G is  $-O-$ ; T is  $-CH_2CH(NH_2)-$ ;  $R^1$  and  $R^2$  are each iodo;  $R^4$  is selected from the group consisting of hydrogen and iodo;  $R^5$  is  $-OH$ ; and  $R^3$  is iodo.
31. The compound of claim 27 wherein G is  $-O-$ ; T is  $-N(H)C(O)-$ ;  $R^1$  and  $R^2$  are each methyl;  $R^4$  is hydrogen;  $R^5$  is  $-OH$ ; and  $R^3$  is  $-CH(OH)(4-fluorophenyl)$ .
32. The compound of claim 27 wherein G is  $-CH_2-$ ; T is  $-OCH_2-$ ;  $R^1$  and  $R^2$  are each methyl;  $R^4$  is hydrogen;  $R^5$  is  $-OH$ ; and  $R^3$  is *iso*-propyl.
33. The compound of claim 27 wherein G is  $-O-$ ; T is  $-CH_2-$ ;  $R^1$  and  $R^2$  are each chloro;  $R^4$  is hydrogen;  $R^5$  is  $-OH$ ; and  $R^3$  is *iso*-propyl.

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34. The compound of claim 27 wherein G is -O-; T is -CH<sub>2</sub>CH<sub>2</sub>-; R<sup>1</sup> and R<sup>2</sup> are each chloro; R<sup>4</sup> is hydrogen; R<sup>5</sup> is -OH; and R<sup>3</sup> is *iso*-propyl.

35. A compound of Formula XVI:



wherein:

G is selected from the group consisting of -O-, -S-, -Se-, -S(=O)-, -S(=O)<sub>2</sub>-, -Se-, -CH<sub>2</sub>-, -CF<sub>2</sub>-, -CHF-, -C(O)-, -CH(OH)-, -CH(C<sub>1</sub>-C<sub>4</sub> alkyl)-, -CH(C<sub>1</sub>-C<sub>4</sub> alkoxy)-, -C(=CH<sub>2</sub>)-, -NH-, and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)-, or CH<sub>2</sub> linked to any of the preceding groups;

or G is R<sup>50</sup>-R<sup>51</sup> wherein;

R<sup>50</sup>-R<sup>51</sup> together are -C(R<sup>52</sup>)=C(R<sup>52</sup>)- or alternatively R<sup>50</sup> and R<sup>51</sup> are independently selected from O, S and -CH(R<sup>53</sup>)-, with the provisos that at least one R<sup>50</sup> and R<sup>51</sup> is -CH(R<sup>53</sup>)-, and when one of R<sup>50</sup> and R<sup>51</sup> is O or S, then R<sup>53</sup> is R<sup>54</sup>;

R<sup>54</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

R<sup>53</sup> is selected from hydrogen, halogen, hydroxyl, mercapto, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio; and

R<sup>52</sup> is selected from hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl,

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fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

A and T are each independently selected from the group consisting of  $-(CR^a)_2-$ ,  $-(CR^a)_2$ ,  $-O(CR^b)_2-$ ,  $-S(CR^b)_2-$ ,  $-N(R^c)(CR^b)_2-$ ,  $-N(R^b)C(O)-$ ,  $-C(O)(CR^b)_2-$ ,  $-(CR^b)_2C(O)-$ ,  $-(CR^b)_2O-$ ,  $-(CR^b)_2S-$ , and  $-(CR^b)_2N(R^c)-$ ;

Each  $R^a$  is independently selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_4$  alkyl, halogen,  $-OH$ , optionally substituted  $-O-C_1-C_4$  alkyl,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-S-C_1-C_4$  alkyl,  $-NR^cR^e$ , optionally substituted  $-C_2-C_4$  alkenyl, and optionally substituted  $-C_2-C_4$  alkynyl; with the proviso that when one  $R^a$  is attached to C through an O, S, or N atom, then the other  $R^a$  attached to the same C is a hydrogen, or attached via a carbon atom;

Each  $R^b$  is independently selected from the group consisting of hydrogen and optionally substituted  $-C_1-C_4$  alkyl;

Each  $R^c$  is independently selected from the group consisting of hydrogen and optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-C(O)-C_1-C_4$  alkyl, and  $-C(O)H$ ;

$R^1$ ,  $R^2$ , and  $R^7$  are each independently selected from the group consisting of hydrogen, halogen, optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-S-C_1-C_3$  alkyl, optionally substituted  $-C_2-C_4$  alkenyl, optionally substituted  $-C_2-C_4$  alkynyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-O-C_1-C_3$  alkyl, and cyano; with the proviso that at least one of  $R^1$  and  $R^2$  is not hydrogen;

$R^8$  and  $R^9$  are each independently selected from the group consisting of hydrogen, halogen, optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-S-C_1-C_3$  alkyl, optionally substituted  $-C_2-C_4$  alkenyl, optionally substituted  $-C_2-C_4$  alkynyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-O-C_1-C_3$  alkyl, hydroxy,  $-(CR^a)_2$ aryl,  $-(CR^a)_2$ cycloalkyl,  $-(CR^a)_2$ heterocycloalkyl,  $-C(O)aryl$ ,  $-C(O)cycloalkyl$ ,  $-C(O)heterocycloalkyl$ ,  $-C(O)alkyl$  and cyano;

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$R^3$  and  $R^4$  are each independently selected from the group consisting of hydrogen, halogen,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , cyano, optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^a_2)_m$ aryl, optionally substituted  $-(CR^a_2)_m$ cycloalkyl, optionally substituted  $-(CR^a_2)_m$ heterocycloalkyl,  $-C(R^b)=C(R^b)$ -aryl,  $-C(R^b)=C(R^b)$ -cycloalkyl,  $-C(R^b)=C(R^b)$ -heterocycloalkyl,  $-C\equiv C$ (aryl),  $-C\equiv C$ (cycloalkyl),  $-C\equiv C$ (heterocycloalkyl),  $-(CR^a_2)_h(CR^b_2)NR^fR^g$ ,  $-OR^d$ ,  $-SR^d$ ,  $-S(=O)R^e$ ,  $-S(=O)_2R^e$ ,  $-S(=O)_2NR^fR^g$ ,  $-C(O)NR^fR^g$ ,  $-C(O)OR^h$ ,  $-C(O)R^e$ ,  $-N(R^b)C(O)R^e$ ,  $-N(R^b)C(O)NR^fR^g$ ,  $-N(R^b)S(=O)_2R^e$ ,  $-N(R^b)S(=O)_2NR^fR^g$ , and  $-NR^fR^g$ ;

Each  $R^d$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b_2)_h$ aryl, optionally substituted  $-(CR^b_2)_h$ cycloalkyl, optionally substituted  $-(CR^b_2)_h$ heterocycloalkyl, and  $-C(O)NR^fR^g$ ;

Each  $R^e$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^a_2)_h$ aryl, optionally substituted  $-(CR^a_2)_h$ cycloalkyl, and optionally substituted  $-(CR^a_2)_h$ heterocycloalkyl;

$R^f$  and  $R^g$  are each independently selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b_2)_h$ aryl, optionally substituted  $-(CR^b_2)_h$ cycloalkyl, and optionally substituted  $-(CR^b_2)_h$ heterocycloalkyl, or  $R^f$  and  $R^g$  may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4 unsaturations, said heterocyclic ring may contain a second heterogroup within the ring selected from the group consisting of O,  $NR^e$ , and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally

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substituted -C<sub>1</sub>-C<sub>4</sub> alkyl, -OR<sup>b</sup>, oxo, cyano, -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, optionally substituted phenyl, and -C(O)OR<sup>b</sup>;

Each R<sup>b</sup> is selected from the group consisting of optionally substituted -C<sub>1</sub>-C<sub>12</sub> alkyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkenyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkynyl, optionally substituted -(CR<sup>b</sup>)<sub>n</sub>aryl, optionally substituted -(CR<sup>b</sup>)<sub>n</sub>cycloalkyl, and optionally substituted -(CR<sup>b</sup>)<sub>n</sub>heterocycloalkyl; or

R<sup>3</sup> and R<sup>8</sup> are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which R<sup>3</sup> and R<sup>8</sup> are attached, including 0 to 2 heteroatoms independently selected from -NR<sup>b</sup>, -O-, and -S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; or

R<sup>8</sup> and G are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring comprising -CH=CH-CH=, -N=CH-CH=, -CH=N-CH= or -CH=CH-N=;

R<sup>5</sup> is selected from the group consisting of -OH, optionally substituted -OC<sub>1</sub>-C<sub>6</sub> alkyl, -OC(O)R<sup>6</sup>, -OC(O)OR<sup>b</sup>, -NHC(O)OR<sup>b</sup>, -OC(O)NH(R<sup>b</sup>), -F, -NHC(O)R<sup>6</sup>, -NHS(=O)R<sup>6</sup>, -NHS(=O)<sub>2</sub>R<sup>6</sup>, -NHC(=S)NH(R<sup>b</sup>), and -NHC(O)NH(R<sup>b</sup>); or

R<sup>3</sup> and R<sup>5</sup> are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which R<sup>3</sup> and R<sup>5</sup> are attached, including 0 to 2 heteroatoms independently selected from -NR<sup>b</sup>, -O-, and -S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

Y is selected from the group consisting of -O-, and -NR<sup>v</sup>;

when Y is -O-, R<sup>11</sup> attached to -O- is independently selected from the group consisting of -H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH<sub>2</sub>-heterocycloalkyl wherein the

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cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl,  $-C(R^2)_2OC(O)NR^2_2$ ,  $-NR^2-C(O)-R^y$ ,  $-C(R^2)_2-OC(O)R^y$ ,  $-C(R^2)_2-O-C(O)OR^y$ ,  $-C(R^2)_2OC(O)SR^y$ ,  $-alkyl-S-C(O)R^y$ ,  $-alkyl-S-S-alkylhydroxy$ , and  $-alkyl-S-S-S-alkylhydroxy$ ;

when Y is  $-NR^y$ -, then  $R^{11}$  attached to  $-NR^y$ - is independently selected from the group consisting of -H,  $-[C(R^2)_2]_q-C(O)OR^y$ ,  $-C(R^2)_2C(O)OR^y$ ,  $-[C(R^2)_2]_q-C(O)SR^y$ , and  $-cycloalkylene-C(O)OR^y$ ;

q is an integer 2 or 3;

Each  $R^2$  is selected from the group consisting of  $R^y$  and -H;

Each  $R^y$  is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

Each  $R^x$  is independently selected from the group consisting of -H, and alkyl, or together  $R^x$  and  $R^x$  form a cycloalkyl group;

Each  $R^y$  is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

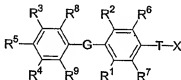
and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

36. The compound of claim 35 wherein  $R^7$  is selected from the group consisting of hydrogen, halogen,  $-C_1-C_4$  alkyl, cyano and  $CF_3$ .
37. The compound of claim 36 wherein  $R^7$  is hydrogen, halogen, or methyl.
38. The compound of claim 35 wherein  $R^8$  and  $R^9$  are independently selected from the group consisting of hydrogen, halogen,  $-C_1-C_4$  alkyl,  $-C_1-C_4$  alkylaryl, cyano and  $CF_3$ .



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39. The compound of claim 38 wherein  $R^8$  and  $R^9$  are independently hydrogen, halogen, methyl, benzyl, and benzoate.
40. A compound of Formula XVII:



wherein:

G is selected from the group consisting of -O-, -S-, -Se-, -S(=O)-, -S(=O)<sub>2</sub>-, -Se-, -CH<sub>2</sub>-, -CF<sub>2</sub>-, -CHF-, -C(O)-, -CH(OH)-, -CH(C<sub>1</sub>-C<sub>4</sub> alkyl)-, -CH(C<sub>1</sub>-C<sub>4</sub> alkoxy)-, -C(=CH<sub>2</sub>)-, -NH-, and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)-, or CH<sub>2</sub> linked to any of the preceding groups;

or G is R<sup>50</sup>-R<sup>51</sup> wherein;

R<sup>50</sup>-R<sup>51</sup> together are -C(R<sup>53</sup>)=C(R<sup>52</sup>)- or alternatively R<sup>50</sup> and R<sup>51</sup> are independently selected from O, S and -CH(R<sup>53</sup>)-, with the provisos that at least one R<sup>50</sup> and R<sup>51</sup> is -CH(R<sup>53</sup>)-, and when one of R<sup>50</sup> and R<sup>51</sup> is O or S, then R<sup>53</sup> is R<sup>54</sup>;

R<sup>54</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

R<sup>53</sup> is selected from hydrogen, halogen, hydroxyl, mercapto, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio; and

R<sup>52</sup> is selected from hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

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T is selected from the group consisting of  $-(\text{CR}^a)_n\text{C}(\text{R}^b)_2\text{O}-$ ,  $-(\text{CR}^a)_n\text{C}(\text{R}^b)_2\text{N}(\text{R}^c)-$ ,  $-(\text{CR}^a)_n\text{C}(\text{R}^b)_2\text{S}-$ ,  $-\text{C}(\text{O})(\text{CR}^a)_n\text{C}(\text{R}^b)_2\text{O}-$ ,  $-\text{C}(\text{O})(\text{CR}^a)_p\text{C}(\text{R}^b)_2\text{N}(\text{R}^c)-$ ,  $-\text{C}(\text{O})(\text{CR}^a)_p\text{C}(\text{R}^b)_2\text{S}-$ ,  $-(\text{CR}^a)_p\text{C}(\text{O})\text{C}(\text{R}^b)_2\text{O}-$ ,  $-(\text{CR}^a)_p\text{C}(\text{O})\text{C}(\text{R}^b)_2\text{N}(\text{R}^c)-$ , and  $-(\text{CR}^a)_p\text{C}(\text{O})\text{C}(\text{R}^b)_2\text{S}-$ ;

k is an integer from 0-4;

m is an integer from 0-3;

n is an integer from 0-2;

p is an integer from 0-1;

Each  $\text{R}^a$  is independently selected from the group consisting of hydrogen, optionally substituted  $-\text{C}_1\text{-C}_4$  alkyl, halogen,  $-\text{OH}$ , optionally substituted  $-\text{O}-\text{C}_1\text{-C}_4$  alkyl,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{F}$ , optionally substituted  $-\text{S}-\text{C}_1\text{-C}_4$  alkyl,  $-\text{NR}^b\text{R}^c$ , optionally substituted  $-\text{C}_2\text{-C}_4$  alkenyl, and optionally substituted  $-\text{C}_2\text{-C}_4$  alkynyl; with the proviso that when one  $\text{R}^a$  is attached to C through an O, S, or N atom, then the other  $\text{R}^a$  attached to the same C is a hydrogen, or attached via a carbon atom;

Each  $\text{R}^b$  is independently selected from the group consisting of hydrogen and optionally substituted  $-\text{C}_1\text{-C}_4$  alkyl;

Each  $\text{R}^c$  is independently selected from the group consisting of hydrogen and optionally substituted  $-\text{C}_1\text{-C}_4$  alkyl, optionally substituted  $-\text{C}(\text{O})-\text{C}_1\text{-C}_4$  alkyl, and  $-\text{C}(\text{O})\text{H}$ ;

$\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^6$ , and  $\text{R}^7$  are each independently selected from the group consisting of hydrogen, halogen, optionally substituted  $-\text{C}_1\text{-C}_4$  alkyl, optionally substituted  $-\text{S}-\text{C}_1\text{-C}_3$  alkyl, optionally substituted  $-\text{C}_2\text{-C}_4$  alkenyl, optionally substituted  $-\text{C}_2\text{-C}_4$  alkynyl,  $-\text{CF}_3$ ,  $-\text{CHF}_2$ ,  $-\text{CH}_2\text{F}$ ,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{F}$ , optionally substituted  $-\text{O}-\text{C}_1\text{-C}_3$  alkyl, and cyano; with the proviso that at least one of  $\text{R}^1$  and  $\text{R}^2$  is not hydrogen;

$\text{R}^8$  and  $\text{R}^9$  are each independently selected from the group consisting of hydrogen, halogen, optionally substituted  $-\text{C}_1\text{-C}_4$  alkyl, optionally substituted  $-\text{S}-\text{C}_1\text{-C}_3$  alkyl, optionally substituted  $-\text{C}_2\text{-C}_4$  alkenyl, optionally substituted  $-\text{C}_2\text{-C}_4$  alkynyl,  $-\text{CF}_3$ ,  $-\text{CHF}_2$ ,  $-\text{CH}_2\text{F}$ ,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{F}$ , optionally substituted  $-\text{O}-\text{C}_1\text{-C}_3$  alkyl, hydroxy,  $-(\text{CR}^a)_2\text{aryl}$ ,  $-(\text{CR}^a)_2\text{cycloalkyl}$ ,

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-(CR<sup>a</sup>)heterocycloalkyl, -C(O)aryl, -C(O)cycloalkyl, -C(O)heterocycloalkyl, -C(O)alkyl and cyano; or

R<sup>i</sup> is selected from the group consisting of hydrogen, -C(O)C<sub>1</sub>-C<sub>4</sub> alkyl, and -C<sub>1</sub>-C<sub>4</sub> alkyl; or

R<sup>1</sup> and R<sup>7</sup> are taken together along with the carbons to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which R<sup>1</sup> and R<sup>7</sup> are attached, including 0 to 2 heteroatoms independently selected from -NR<sup>b</sup>, -O-, and -S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of hydrogen, halogen, -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>F, cyano, optionally substituted -C<sub>1</sub>-C<sub>12</sub> alkyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkenyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkynyl, optionally substituted -(CR<sup>a</sup>)<sub>m</sub>aryl, optionally substituted -(CR<sup>a</sup>)<sub>m</sub>cycloalkyl, optionally substituted -(CR<sup>a</sup>)<sub>m</sub>heterocycloalkyl, -C(R<sup>b</sup>)=C(R<sup>b</sup>)-aryl, -C(R<sup>b</sup>)=C(R<sup>b</sup>)-cycloalkyl, -C(R<sup>b</sup>)=C(R<sup>b</sup>)-heterocycloalkyl, -C≡C(aryl), -C≡C(cycloalkyl), -C≡C(heterocycloalkyl), -(CR<sup>a</sup>)<sub>n</sub>(CR<sup>b</sup>)NR<sup>f</sup>R<sup>g</sup>, -OR<sup>d</sup>, -SR<sup>d</sup>, -S(=O)R<sup>e</sup>, -S(=O)<sub>2</sub>R<sup>e</sup>, -S(=O)<sub>2</sub>NR<sup>f</sup>R<sup>g</sup>, -C(O)NR<sup>f</sup>R<sup>g</sup>, -C(O)OR<sup>h</sup>, -C(O)R<sup>e</sup>, -N(R<sup>b</sup>)C(O)R<sup>e</sup>, -N(R<sup>b</sup>)C(O)NR<sup>f</sup>R<sup>g</sup>, -N(R<sup>b</sup>)S(=O)<sub>2</sub>R<sup>e</sup>, -N(R<sup>b</sup>)S(=O)<sub>2</sub>NR<sup>f</sup>R<sup>g</sup>, and -NR<sup>f</sup>R<sup>g</sup>;

Each R<sup>d</sup> is selected from the group consisting of optionally substituted -C<sub>1</sub>-C<sub>12</sub> alkyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkenyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkynyl, optionally substituted -(CR<sup>b</sup>)<sub>n</sub>aryl, optionally substituted -(CR<sup>b</sup>)<sub>n</sub>cycloalkyl, optionally substituted -(CR<sup>b</sup>)<sub>n</sub>heterocycloalkyl, and -C(O)NR<sup>f</sup>R<sup>g</sup>;

Each R<sup>e</sup> is selected from the group consisting of optionally substituted -C<sub>1</sub>-C<sub>12</sub> alkyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkenyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkynyl, optionally substituted -(CR<sup>a</sup>)<sub>n</sub>aryl, optionally substituted -(CR<sup>a</sup>)<sub>n</sub>cycloalkyl, and optionally substituted -(CR<sup>a</sup>)<sub>n</sub>heterocycloalkyl;

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$R^f$  and  $R^g$  are each independently selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, and optionally substituted  $-(CR^b)_n$ heterocycloalkyl, or  $R^f$  and  $R^g$  may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4 unsaturations, said heterocyclic ring may contain a second heterogroup within the ring selected from the group consisting of O,  $NR^c$ , and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally substituted  $-C_1-C_4$  alkyl,  $-OR^b$ , oxo, cyano,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ , optionally substituted phenyl, and  $-C(O)OR^h$ ;

Each  $R^h$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, and optionally substituted  $-(CR^b)_n$ heterocycloalkyl; or

$R^3$  and  $R^8$  are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^3$  and  $R^8$  are attached, including 0 to 2 heteroatoms independently selected from  $-NR^h$ ,  $-O-$ , and  $-S-$ , with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; or

$R^8$  and G are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring comprising  $-CH=CH-CH=$ ,  $-N=CH-CH=$ ,  $-CH=N-CH=$  or  $-CH=CH-N=$ ;

$R^5$  is selected from the group consisting of  $-OH$ , optionally substituted  $-OC_1-C_6$  alkyl,  $-OC(O)R^e$ ,  $-OC(O)OR^b$ ,  $-NHC(O)OR^b$ ,  $-OC(O)NH(R^b)$ ,  $-F$ ,  $-NHC(O)R^e$ ,  $-NHS(=O)R^e$ ,  $-NHS(=O)_2R^e$ ,  $-NHC(=S)NH(R^b)$ , and  $-NHC(O)NH(R^b)$ ; or

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$R^3$  and  $R^5$  are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^3$  and  $R^5$  are attached, including 0 to 2 heteroatoms independently selected from  $-NR^h$ ,  $-O-$ , and  $-S-$ , with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

X is  $P(O)(YR^{11})Y''$ ;

$Y''$  is selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_6$ -alkyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-CH_2OH$ , optionally substituted  $-C_2-C_6$  alkenyl, optionally substituted  $-C_2-C_6$  alkynyl, optionally substituted  $-(CR^a)_n$ cycloalkyl, optionally substituted  $(CR^a)_n$ heterocycloalkyl,  $-(CR^a)_kS(=O)R^e$ ,  $-(CR^a)_kS(=O)_2R^e$ ,  $-(CR^a)_kS(=O)_2NR^fR^g$ ,  $-(CR^a)_kC(O)NR^fR^g$ , and  $-(CR^a)_kC(O)R^e$ ;

Y is selected from the group consisting of  $-O-$ , and  $-NR^v$ ;

when Y is  $-O-$ ,  $R^{11}$  attached to  $-O-$  is selected from the group consisting of higher alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted  $CH_2$ -heterocycloalkyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted  $-alkylaryl$ ,  $-C(R^3)_2OC(O)NR^z$ ,  $-NR^z-C(O)-R^y$ ,  $-C(R^3)_2OC(O)R^y$ ,  $-C(R^3)_2-O-C(O)OR^y$ ,  $-C(R^3)_2OC(O)SR^y$ ,  $-alkyl-S-C(O)R^y$ ,  $-alkyl-S-S-alkylhydroxy$ , and  $-alkyl-S-S-S-alkylhydroxy$ ;

when Y is  $-NR^v$ , then  $R^{11}$  attached to  $-NR^v$  is selected from the group consisting of  $-H$ ,  $-[C(R^3)_2]_q-C(O)OR^y$ ,  $-C(R^3)_2C(O)OR^y$ ,  $-[C(R^3)_2]_q-C(O)SR^y$ , and  $-cycloalkylene-C(O)OR^y$ ;

q is an integer 2 or 3;

Each  $R^z$  is selected from the group consisting of  $R^y$  and  $-H$ ;

Each  $R^y$  is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

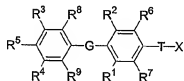
Each  $R^x$  is independently selected from the group consisting of  $-H$ , and alkyl, or together  $R^x$  and  $R^x$  form a cycloalkyl group;

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Each R<sup>v</sup> is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

41. A compound of Formula XVII:



wherein:

G is selected from the group consisting of -O-, -S-, -Se-, -S(=O)-, -S(=O)<sub>2</sub>-, -Se-, -CH<sub>2</sub>-, -CF<sub>2</sub>-, -CHF-, -C(O)-, -CH(OH)-, -CH(C<sub>1</sub>-C<sub>4</sub> alkyl)-, -CH(C<sub>1</sub>-C<sub>4</sub> alkoxy)-, -C(=CH<sub>2</sub>)-, -NH-, and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)-, or CH<sub>2</sub> linked to any of the preceding groups;

or G is R<sup>50</sup>-R<sup>51</sup> wherein;

R<sup>50</sup>-R<sup>51</sup> together are -C(R<sup>52</sup>)=C(R<sup>53</sup>)- or alternatively R<sup>50</sup> and R<sup>51</sup> are independently selected from O, S and -CH(R<sup>53</sup>)-, with the provisos that at least one R<sup>50</sup> and R<sup>51</sup> is -CH(R<sup>53</sup>)-, and when one of R<sup>50</sup> and R<sup>51</sup> is O or S, then R<sup>53</sup> is R<sup>54</sup>;

R<sup>54</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, fluoromethyl, difluoromethyl, or trifluoromethyl;

R<sup>53</sup> is selected from hydrogen, halogen, hydroxyl, mercapto, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio; and

R<sup>52</sup> is selected from hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methylthio, fluoromethylthio, difluoromethylthio and trifluoromethylthio;

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T is selected from the group consisting of  $-(CR^a)_n C(R^b)_2 O-$ ,  $-(CR^a)_n C(R^b)_2 N(R^b)-$ ,  $-(CR^a)_n C(R^b)_2 S-$ ,  $-C(O)(CR^a)_p C(R^b)_2 O-$ ,  $-C(O)(CR^a)_p C(R^b)_2 N(R^b)-$ ,  $-C(O)(CR^a)_p C(R^b)_2 S-$ ,  $-(CR^a)_p C(O)C(R^b)_2 O-$ ,  $-(CR^a)_p C(O)C(R^b)_2 N(R^b)-$ , and  $-(CR^a)_p C(O)C(R^b)_2 S-$ ;

k is an integer from 0-4;

m is an integer from 0-3;

n is an integer from 0-2;

p is an integer from 0-1;

Each  $R^a$  is independently selected from the group consisting of hydrogen, optionally substituted  $-C_1-C_4$  alkyl, halogen,  $-OH$ , optionally substituted  $-O-C_1-C_4$  alkyl,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-S-C_1-C_4$  alkyl,  $-NR^b R^c$ , optionally substituted  $-C_2-C_4$  alkenyl, and optionally substituted  $-C_2-C_4$  alkynyl; with the proviso that when one  $R^a$  is attached to C through an O, S, or N atom, then the other  $R^a$  attached to the same C is a hydrogen, or attached via a carbon atom;

Each  $R^b$  is independently selected from the group consisting of hydrogen and optionally substituted  $-C_1-C_4$  alkyl;

Each  $R^c$  is independently selected from the group consisting of hydrogen and optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-C(O)-C_1-C_4$  alkyl, and  $-C(O)H$ ;

$R^1$ ,  $R^2$ ,  $R^6$ , and  $R^7$  are each independently selected from the group consisting of hydrogen, halogen, optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-S-C_1-C_3$  alkyl, optionally substituted  $-C_2-C_4$  alkenyl, optionally substituted  $-C_2-C_4$  alkynyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-O-C_1-C_3$  alkyl, and cyano; with the proviso that at least one of  $R^1$  and  $R^2$  is not hydrogen;

$R^8$  and  $R^9$  are each independently selected from the group consisting of hydrogen, halogen, optionally substituted  $-C_1-C_4$  alkyl, optionally substituted  $-S-C_1-C_3$  alkyl, optionally substituted  $-C_2-C_4$  alkenyl, optionally substituted  $-C_2-C_4$  alkynyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ , optionally substituted  $-O-C_1-C_3$  alkyl, hydroxy,  $-(CR^a)_2$ aryl,  $-(CR^a)_2$ cycloalkyl,

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-(CR<sup>a</sup><sub>2</sub>)heterocycloalkyl, -C(O)aryl, -C(O)cycloalkyl, -C(O)heterocycloalkyl, -C(O)alkyl and cyano; or

R<sup>1</sup> and R<sup>7</sup> are taken together along with the carbons to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which R<sup>1</sup> and R<sup>7</sup> are attached, including 0 to 2 heteroatoms independently selected from -NR<sup>h</sup>-, -O-, and -S-, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of hydrogen, halogen, -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>F, cyano, optionally substituted -C<sub>1</sub>-C<sub>12</sub> alkyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkenyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkynyl, optionally substituted -(CR<sup>a</sup><sub>2</sub>)<sub>n</sub>aryl, optionally substituted -(CR<sup>a</sup><sub>2</sub>)<sub>n</sub>cycloalkyl, optionally substituted -(CR<sup>a</sup><sub>2</sub>)<sub>n</sub>heterocycloalkyl, -C(R<sup>b</sup>)=C(R<sup>b</sup>)-aryl, -C(R<sup>b</sup>)=C(R<sup>b</sup>)-cycloalkyl, -C(R<sup>b</sup>)=C(R<sup>b</sup>)-heterocycloalkyl, -C≡C(aryl), -C≡C(cycloalkyl), -C≡C(heterocycloalkyl), -(CR<sup>a</sup><sub>2</sub>)<sub>n</sub>(CR<sup>b</sup><sub>2</sub>)NR<sup>f</sup>R<sup>g</sup>, -OR<sup>d</sup>, -SR<sup>d</sup>, -S(=O)R<sup>e</sup>, -S(=O)<sub>2</sub>R<sup>e</sup>, -S(=O)<sub>2</sub>NR<sup>f</sup>R<sup>g</sup>, -C(O)NR<sup>f</sup>R<sup>g</sup>, -C(O)OR<sup>h</sup>, -C(O)R<sup>e</sup>, -N(R<sup>b</sup>)C(O)R<sup>e</sup>, -N(R<sup>b</sup>)C(O)NR<sup>f</sup>R<sup>g</sup>, -N(R<sup>b</sup>)S(=O)<sub>2</sub>R<sup>e</sup>, -N(R<sup>b</sup>)S(=O)<sub>2</sub>NR<sup>f</sup>R<sup>g</sup>, and -NR<sup>f</sup>R<sup>g</sup>;

Each R<sup>d</sup> is selected from the group consisting of optionally substituted -C<sub>1</sub>-C<sub>12</sub> alkyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkenyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkynyl, optionally substituted -(CR<sup>b</sup><sub>2</sub>)<sub>n</sub>aryl, optionally substituted -(CR<sup>b</sup><sub>2</sub>)<sub>n</sub>cycloalkyl, optionally substituted -(CR<sup>b</sup><sub>2</sub>)<sub>n</sub>heterocycloalkyl, and -C(O)NR<sup>f</sup>R<sup>g</sup>;

Each R<sup>e</sup> is selected from the group consisting of optionally substituted -C<sub>1</sub>-C<sub>12</sub> alkyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkenyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub> alkynyl, optionally substituted -(CR<sup>a</sup><sub>2</sub>)<sub>n</sub>aryl, optionally substituted -(CR<sup>a</sup><sub>2</sub>)<sub>n</sub>cycloalkyl, and optionally substituted -(CR<sup>a</sup><sub>2</sub>)<sub>n</sub>heterocycloalkyl;

R<sup>f</sup> and R<sup>g</sup> are each independently selected from the group consisting of hydrogen, optionally substituted -C<sub>1</sub>-C<sub>12</sub> alkyl, optionally substituted -C<sub>2</sub>-C<sub>12</sub>



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alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, and optionally substituted  $-(CR^b)_n$ heterocycloalkyl, or  $R^f$  and  $R^g$  may together form an optionally substituted heterocyclic ring of 3-8 atoms containing 0-4 unsaturations, said heterocyclic ring may contain a second heterogroup within the ring selected from the group consisting of O,  $NR^c$ , and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally substituted  $-C_1-C_4$  alkyl,  $-OR^b$ , oxo, cyano,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ , optionally substituted phenyl, and  $-C(O)OR^b$ ;

Each  $R^h$  is selected from the group consisting of optionally substituted  $-C_1-C_{12}$  alkyl, optionally substituted  $-C_2-C_{12}$  alkenyl, optionally substituted  $-C_2-C_{12}$  alkynyl, optionally substituted  $-(CR^b)_n$ aryl, optionally substituted  $-(CR^b)_n$ cycloalkyl, and optionally substituted  $-(CR^b)_n$ heterocycloalkyl; or

$R^3$  and  $R^8$  are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^3$  and  $R^8$  are attached, including 0 to 2 heteroatoms independently selected from  $-NR^h$ ,  $-O-$ , and  $-S-$ , with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; or

$R^8$  and G are taken together along with the carbon atoms to which they are attached to form an optionally substituted ring comprising  $-CH=CH-CH=$ ,  $-N=CH-CH=$ ,  $-CH=N-CH=$  or  $-CH=CH-N=$ ;

$R^5$  is selected from the group consisting of  $-OH$ , optionally substituted  $-OC_1-C_6$  alkyl,  $-OC(O)R^e$ ,  $-OC(O)OR^h$ ,  $-NHC(O)OR^h$ ,  $-OC(O)NH(R^b)$ ,  $-F$ ,  $-NHC(O)R^e$ ,  $-NHS(=O)R^e$ ,  $-NHS(=O)_2R^e$ ,  $-NHC(=S)NH(R^b)$ , and  $-NHC(O)NH(R^b)$ ; or

$R^3$  and  $R^5$  are taken together along with the carbons they are attached to form an optionally substituted ring of 5 to 6 atoms with 0-2 unsaturations, not including the unsaturation on the ring to which  $R^3$  and  $R^5$  are attached,

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including 0 to 2 heteroatoms independently selected from  $\text{-NR}^h$ -,  $\text{-O-}$ , and  $\text{-S-}$ , with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom;

X is  $\text{P(O)(YR}^{11}\text{)Y}''$ ;

$\text{Y}''$  is selected from the group consisting of hydrogen, optionally substituted  $\text{-C}_1\text{-C}_6\text{-alkyl}$ ,  $\text{-CF}_3$ ,  $\text{-CHF}_2$ ,  $\text{-CH}_2\text{F}$ ,  $\text{-CH}_2\text{OH}$ , optionally substituted  $\text{-C}_2\text{-C}_6$  alkenyl, optionally substituted  $\text{-C}_2\text{-C}_6$  alkynyl, optionally substituted  $\text{-(CR}^a\text{)}_n\text{cycloalkyl}$ , optionally substituted  $\text{(CR}^a\text{)}_n\text{heterocycloalkyl}$ ,  $\text{-(CR}^a\text{)}_k\text{S(=O)R}^e$ ,  $\text{-(CR}^a\text{)}_k\text{S(=O)}_2\text{R}^e$ ,  $\text{-(CR}^a\text{)}_k\text{S(=O)}_2\text{NR}^f\text{R}^g$ ,  $\text{-(CR}^a\text{)}_k\text{C(O)NR}^f\text{R}^g$ , and  $\text{-(CR}^a\text{)}_k\text{C(O)R}^e$ ;

Y is selected from the group consisting of  $\text{-O-}$ , and  $\text{-NR}^f$ -;

when Y is  $\text{-O-}$ ,  $\text{R}^{11}$  attached to  $\text{-O-}$  is selected from the group consisting of  $\text{-H}$ , alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted  $\text{CH}_2\text{-heterocycloalkyl}$  wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted  $\text{-alkylaryl}$ ,  $\text{-C(R}^2\text{)}_2\text{OC(O)NR}^z$ ,  $\text{-NR}^z\text{-C(O)-R}^y$ ,  $\text{-C(R}^2\text{)}_2\text{-OC(O)R}^y$ ,  $\text{-C(R}^2\text{)}_2\text{-O-C(O)OR}^y$ ,  $\text{-C(R}^2\text{)}_2\text{OC(O)SR}^y$ ,  $\text{-alkyl-S-C(O)R}^y$ ,  $\text{-alkyl-S-S-alkylhydroxy}$ , and  $\text{-alkyl-S-S-S-alkylhydroxy}$ ;

when Y is  $\text{-NR}^f$ -, then  $\text{R}^{11}$  attached to  $\text{-NR}^f$ - is selected from the group consisting of  $\text{-H}$ ,  $\text{-[C(R}^2\text{)}_2]_q\text{-C(O)OR}^y$ ,  $\text{-C(R}^2\text{)}_2\text{C(O)OR}^y$ ,  $\text{-[C(R}^2\text{)}_2]_q\text{-C(O)SR}^y$ , and  $\text{-cycloalkylene-C(O)OR}^y$ ;

q is an integer 2 or 3;

Each  $\text{R}^z$  is selected from the group consisting of  $\text{R}^y$  and  $\text{-H}$ ;

Each  $\text{R}^y$  is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

Each  $\text{R}^x$  is independently selected from the group consisting of  $\text{-H}$ , and alkyl, or together  $\text{R}^x$  and  $\text{R}^x$  form a cycloalkyl group;

Each  $\text{R}^v$  is selected from the group consisting of  $\text{-H}$ , lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

and pharmaceutically acceptable salts and prodrugs thereof and pharmaceutically acceptable salts of said prodrugs.

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42. The compound of any one of claims 1-3, 9, 10, 17, 18, 25-27, 35, 40, or 41 wherein G is selected from the group consisting of -O-, -CH<sub>2</sub>- and R<sup>50</sup>-R<sup>51</sup>.
43. The compound of claims 40 or 41 wherein T is selected from the group consisting of  $-(CR^a)_n C(R^b)_2 O-$ ,  $-(CR^a)_n C(R^b)_2 N(R^b)-$ ,  $-C(O)(CR^a)_p C(R^b)_2 O-$ ,  $-C(O)(CR^a)_p C(R^b)_2 N(R^b)-$ , and  $-(CR^a)_p C(O)C(R^b)_2 O-$ .
44. The compound of claim 43 wherein T is  $-(CR^a)_n C(R^b)_2 O-$ , or  $-C(O)(CR^a)_p C(R^b)_2 O-$ .
45. The compound of any one of claims 1-3, 9, 10, 17, 18, 25-27, 35, 40, or 41 wherein R<sup>1</sup> and R<sup>2</sup> are the same and are selected from the group consisting of halogen, -C<sub>1</sub>-C<sub>4</sub> alkyl, -CF<sub>3</sub>, and cyano.
46. The compound of claim 45 wherein R<sup>1</sup> and R<sup>2</sup> are both alkyl.
47. The compound of any one of claims 1-3, 9, 10, 17, 18, 25-27, 35, 40, or 41 wherein R<sup>1</sup> and R<sup>2</sup> are different and are selected from the group consisting of halogen, -C<sub>1</sub>-C<sub>4</sub> alkyl, -CF<sub>3</sub>, and cyano.
48. The compound of claim 47 wherein R<sup>1</sup> and R<sup>2</sup> are not both halogen.

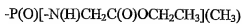
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49. The compound of any one of claims 1-3, 9, 10, 17, 18, 25-27, 35, 40, or 41 wherein  $R^4$  is selected from the group consisting of hydrogen, halogen,  $-C_1-C_4$  alkyl, cyano and  $CF_3$ .
50. The compound of claim 49 wherein  $R^4$  is hydrogen.
51. The compound of any one of claims 25-27, 40, or 41 wherein  $R^6$  and  $R^7$  are independently selected from the group consisting of hydrogen, halogen,  $-C_1-C_4$  alkyl, cyano and  $CF_3$ .
52. The compound of claim 51 wherein  $R^6$  and  $R^7$  are independently hydrogen, halogen, or methyl.
53. The compound of any one of claims 25-27, 40, or 41 wherein  $R^8$  and  $R^9$  are independently selected from the group consisting of hydrogen, halogen,  $-C_1-C_4$  alkyl,  $-C_1-C_4$  alkylaryl, cyano and  $CF_3$ .
54. The compound of claim 53 wherein  $R^8$  and  $R^9$  are independently hydrogen, halogen, methyl, benzyl, and benzoate.
55. The compound of any one of claims 1-3, 9, 10, 17, 18, 25-27, 35, 40, or 41 wherein  $R^5$  is selected from the group consisting of  $-OH$ ,  $-OC(O)R^e$ ,  $-OC(O)OR^h$ ,  $-F$ , and  $-NHC(O)R^e$ .

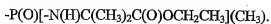
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56. The compound of claim 55 wherein R<sup>5</sup> is -OH.
57. The compound of any one of claims 1-3, 9, 10, 17, 18, 25-27, 35, 40, or 41 wherein R<sup>3</sup> is selected from the group consisting of halogen, optionally substituted -C<sub>1</sub>-C<sub>6</sub> alkyl, -CF<sub>3</sub>, cyano, -C(O)NR<sup>f</sup>R<sup>g</sup>, optionally substituted -(CR<sup>a</sup>)<sub>n</sub>aryl, -SO<sub>2</sub>NR<sup>f</sup>R<sup>g</sup>, and -SO<sub>2</sub>R<sup>c</sup>.
58. The compound of claim 57 wherein R<sup>3</sup> is isopropyl or 4-fluorobenzyl.
59. The compound of any one of claims 1, 9, 17, 25, or 40 wherein X is selected from -P(O)[-OCR<sup>z</sup><sub>2</sub>OC(O)R<sup>y</sup>](Y''), -P(O)[-OCR<sup>z</sup><sub>2</sub>OC(O)OR<sup>y</sup>](Y''), and -P(O)[-N(H)CR<sup>z</sup><sub>2</sub>C(O)OR<sup>y</sup>](Y'').
60. The compound of any one of claims 2, 3, 10, 18, 26, 27, or 41 wherein X is selected from the group consisting of -P(O)(OH)(Y''), -P(O)(OR<sup>y</sup>)(Y''), -P(O)[-OCR<sup>z</sup><sub>2</sub>OC(O)R<sup>y</sup>](Y''), -P(O)[-OCR<sup>z</sup><sub>2</sub>OC(O)OR<sup>y</sup>](Y''), and -P(O)[-N(H)CR<sup>z</sup><sub>2</sub>C(O)OR<sup>y</sup>](Y'').
61. The compound of claim 60 wherein X is selected from the group consisting of -P(O)(OH)(CH<sub>3</sub>), -P(O)(OH)(CH<sub>2</sub>CH<sub>3</sub>), -P(O)[-OCH<sub>2</sub>OC(O)-*t*-butyl](CH<sub>3</sub>), -P(O)[-OCH<sub>2</sub>OC(O)O-*iso*-propyl](CH<sub>3</sub>), P(O)[-OCH(CH<sub>3</sub>)OC(O)-*t*-butyl](CH<sub>3</sub>), -P(O)[-OCH(CH<sub>3</sub>)OC(O)O-*iso*-propyl](CH<sub>3</sub>), -P(O)[-N(H)CH(CH<sub>3</sub>)C(O)OCH<sub>2</sub>CH<sub>3</sub>](CH<sub>3</sub>),

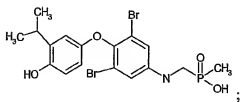
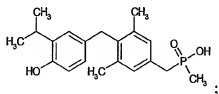
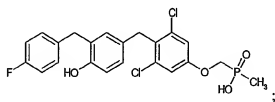
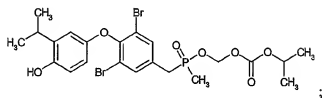
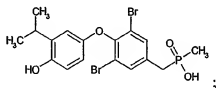
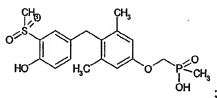
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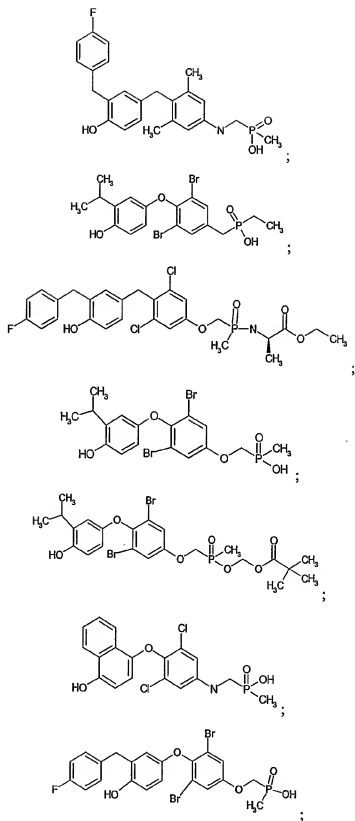
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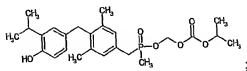
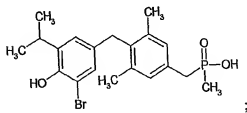
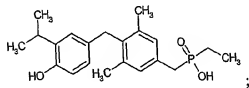
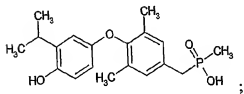
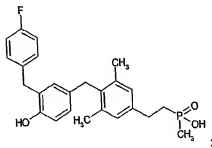
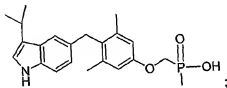
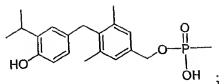
62. A compound selected from the group consisting of:



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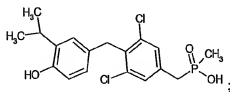
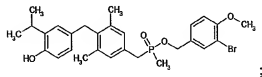
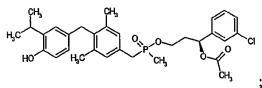
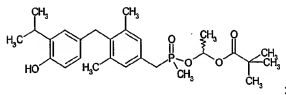
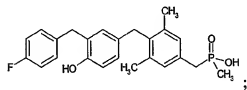
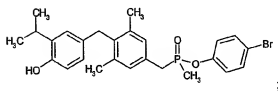
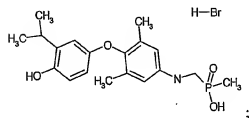
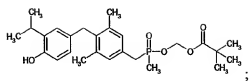


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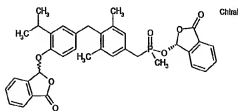
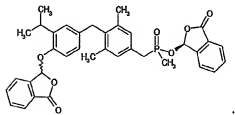
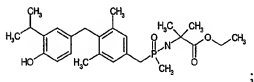
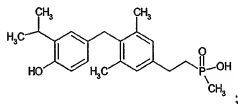
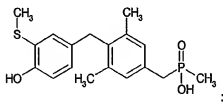
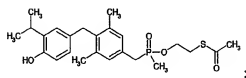
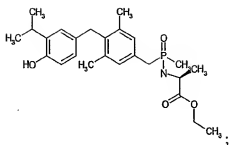




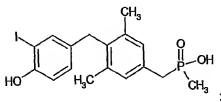
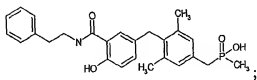
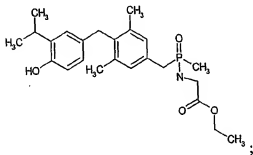
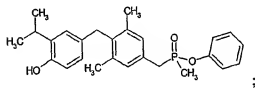
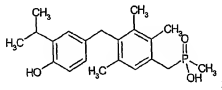
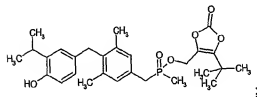
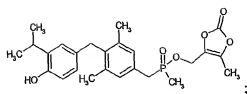
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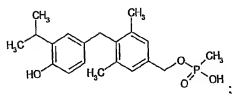
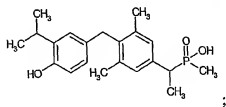
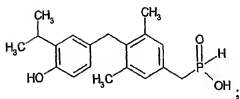
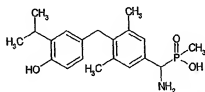
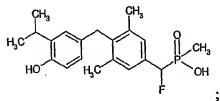
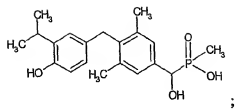
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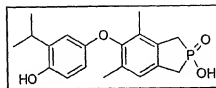
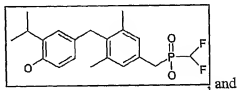
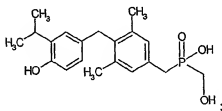
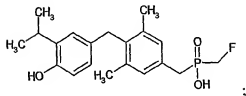
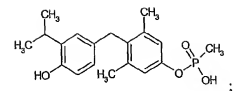
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and pharmaceutically acceptable salts and prodrugs thereof.

63. A compound of any one of claims 1-3, 9, 10, 17, 18, 25-27, 35, 40, 41, or 62, wherein said compound is in the form of a co-crystal.
64. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of any one of claims 1-3, 9, 10, 17, 18, 25-27, 35, 40, 41, or 62.

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65. The pharmaceutical composition of claim 64 wherein said pharmaceutical composition in a form selected from the group consisting of a controlled release composition, transdermal patch, tablet, hard capsule, and soft capsule.
66. The pharmaceutical composition of claim 64 wherein said pharmaceutical composition comprises a crystalline form of said compound.
67. The pharmaceutical composition of claim 64 wherein said pharmaceutical composition comprises a salt form of said compound.
68. The pharmaceutical composition of claim 64 wherein said pharmaceutical composition is administered orally in a unit dose of about 0.375  $\mu\text{g/kg}$  to 3.75  $\text{mg/kg}$ .
69. The pharmaceutical composition of claim 64 wherein said pharmaceutical composition is administered orally in a total daily dose of about 0.375  $\mu\text{g/kg/day}$  to about 3.75  $\text{mg/kg/day}$ , equivalent of the free acid.
70. A method of preventing or treating a metabolic disease comprising administering to an animal a pharmaceutically effective amount of a phosphinic acid-containing compound of any one of claims 1-3, 9, 10, 17, 18, 25-27, 35, 40, 41, or 62, a pharmaceutically acceptable salt

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thereof, or prodrugs thereof or pharmaceutically acceptable salts of said prodrugs, wherein said phosphinic acid-containing compound binds to a thyroid receptor.

71. The method of claim 70 wherein said phosphinic acid-containing compound binds to a thyroid receptor with a  $K_i$  of  $\leq 1 \mu\text{M}$ .
72. The method of claim 71 wherein said thyroid receptor is TR $\alpha$ 1.
73. The method of claim 71 wherein said thyroid receptor is TR $\beta$ 1.
74. The method of claim 71 wherein said phosphinic acid-containing compound binds to a thyroid receptor with a  $K_i$  of  $\leq 100 \text{ nM}$ .
75. The method of claim 74 wherein said thyroid receptor is TR $\alpha$ 1.
76. The method of claim 74 wherein said thyroid receptor is TR $\beta$ 1.
77. The method of claim 70 wherein said metabolic disease is selected from the group consisting of obesity, hypercholesterolemia, hyperlipidemia, atherosclerosis, coronary heart disease, and hypertension.

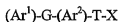
- 679 -

78. The method of claim 77 wherein said metabolic disease is selected from the group consisting of obesity, hypercholesterolemia, and hyperlipidemia.
79. The method of claim 78 wherein said metabolic disease is hypercholesterolemia.
80. The method of claim 70 wherein said metabolic disease is NASH.
81. The method of claim 70 wherein said metabolic disease is selected from the group consisting of impaired glucose tolerance, diabetes, and metabolic syndrome X.
82. The method of claim 70, wherein said phosphinic acid-containing compound activates said thyroid receptor.
83. The method of claim 82 wherein said thyroid receptor is TR $\alpha$ 1.
84. The method of claim 82 wherein said thyroid receptor is TR $\beta$ 1.
85. The method of claim 70 wherein said phosphinic acid- or phosphonic acid monoester-containing compound increases mRNA expression of a gene selected from the group consisting of LDL receptor, ACC, FAS, spot-14, CPT-1, CYP7A, apo AI, and mGPDH.



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86. A method of activating a thyroid receptor in an animal by administering a phosphinic acid-containing compound of any of claims 1-3, 9, 10, 17, 18, 25-27, 35, 40, 41, or 62, a pharmaceutically acceptable salt thereof, or prodrugs thereof or pharmaceutically acceptable salts of said prodrugs, wherein said activation results in the 50% or greater increase in the mRNA expression of a gene selected from the group consisting of LDL receptor, ACC, FAS, spot-14, CPT-1, CYP7A, apo AI, and mGPDH.
87. The method of claim 86 wherein said phosphinic acid-containing compound binds to a thyroid receptor with a  $K_i$  of  $\leq 1 \mu\text{M}$ .
88. The method of claim 97 wherein said phosphinic acid-containing compound binds to a thyroid receptor with a  $K_i$  of  $\leq 100 \text{ nM}$ .
89. A compound of Formula X:



wherein:

$\text{Ar}^1$  and  $\text{Ar}^2$  are aryl groups;

G is an atom or group of atoms that links  $\text{Ar}^1$  and  $\text{Ar}^2$  through a single C, S, Se, O, or N atom or  $\text{CH}_2$  linked to C, S, Se, O, or N, wherein the C or N is substituted;

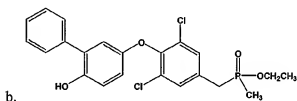
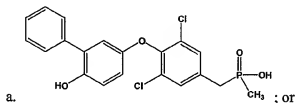
T is an atom or group of atoms linking  $\text{Ar}^2$  to X through 1-4 contiguous atoms or is absent;

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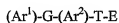
X is a phosphinic acid or prodrug thereof;

wherein said compound has a  $K_i$  of  $\leq 150$  nM relative to T3;

with the provisos that said compound is not:



90. A method of improving liver versus heart selectivity of a thyromimetic compound of Formula Y:



wherein:

$\text{Ar}^1$  and  $\text{Ar}^2$  are aryl groups;

G is an atom or group of atoms that links  $\text{Ar}^1$  and  $\text{Ar}^2$  through a single C, S, Se, O, or N atom or  $\text{CH}_2$  linked to C, S, Se, O, or N, wherein the C or N is substituted;

T is an atom or group of atoms linking  $\text{Ar}^2$  to E through 1-4 contiguous atoms or is absent;

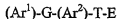
E is selected from the group consisting of a functional group or moiety with a  $\text{pK}_a \leq 7.4$ , a carboxylic acid moiety or an atom or group of atoms

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containing an O or N that binds the thyroid hormone binding pocket of a TR $\alpha$  or TR $\beta$ ,

comprising the step of replacing E with a phosphinic acid or prodrug thereof.

91. A method of increasing the therapeutic index of a thyromimetic compound of Formula Y:



wherein:

Ar<sup>1</sup> and Ar<sup>2</sup> are aryl groups;

G is an atom or group of atoms that links Ar<sup>1</sup> and Ar<sup>2</sup> through a single C, S, Se, O, or N atom or CH<sub>2</sub> linked to C, S, Se, O, or N, wherein the C or N is substituted;

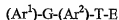
T is an atom or group of atoms linking Ar<sup>2</sup> to E through 1-4 atoms or is absent;

E is selected from the group consisting of a functional group or moiety with a  $\text{pKa} \leq 7.4$ , a carboxylic acid moiety or an atom or group of atoms containing an O or N that binds the thyroid hormone binding pocket of a TR $\alpha$  or TR $\beta$ ,

comprising the step of replacing E with a phosphinic acid or prodrug thereof.

92. A method of designing a thyromimetic compound with improved liver versus heart selectivity comprising the steps of:

obtaining a molecular formula for a thyromimetic of Formula Y:



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wherein:

Ar<sup>1</sup> and Ar<sup>2</sup> are aryl groups;

G is an atom or group of atoms that links Ar<sup>1</sup> and Ar<sup>2</sup> through a single C, S, Se, O, or N atom or CH<sub>2</sub> linked to C, S, Se, O, or N, wherein the C or N is substituted;

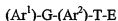
T is an atom or group of atoms linking Ar<sup>2</sup> to E through 1-4 contiguous atoms or is absent;

E is selected from the group consisting of a functional group or moiety with a  $pK_a \leq 7.4$ , a carboxylic acid moiety, or an atom or group of atoms containing an O or N that binds the thyroid hormone binding pocket of a TR $\alpha$  or TR $\beta$ ;

comprising the step of replacing E with a phosphinic acid or prodrug thereof; and synthesizing a compound of Formula X wherein X is a phosphinic acid or prodrug thereof.

93. A method of designing a thyromimetic compound with an improved therapeutic index comprising the steps of:

obtaining a molecular formula for a thyromimetic of Formula Y:



wherein:

Ar<sup>1</sup> and Ar<sup>2</sup> are aryl groups;

G is an atom or group of atoms that links Ar<sup>1</sup> and Ar<sup>2</sup> through a single C, S, Se, O, or N atom or CH<sub>2</sub> linked to C, S, Se, O, or N, wherein the C or N is substituted;

T is an atom or group of atoms linking Ar<sup>2</sup> to E through 1-4 atoms or is absent;

E is selected from the group consisting of a functional group or moiety with a  $pK_a \leq 7.4$ , a carboxylic acid moiety, or an atom or group of atoms

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containing an O or N that binds the thyroid hormone binding pocket of a TR $\alpha$  or TR $\beta$ ;

comprising the step of replacing E with a phosphinic acid or prodrug thereof; and synthesizing a compound of Formula X wherein X is a phosphinic acid or prodrug thereof.

94. A method of increasing the liver specificity of a T3 mimetic having a carboxylic acid moiety comprising the preparation of a compound that is an analog of said T3 mimetic wherein said carboxylic acid moiety is replaced by phosphinic acid or prodrugs thereof.

95. A method of selecting a T3 mimetic having enhanced liver specificity comprising the steps of:

a) measuring the liver specificity of a T3 mimetic having a carboxylic acid moiety;

b) measuring the liver specificity of a compound that is an analog of said T3 mimetic having a carboxylic acid moiety wherein the carboxylic acid moiety is replaced by a phosphinic acid or prodrug thereof; and

comparing the liver specificities of steps a) and b).

96. A method of screening T3 mimetics comprising the steps of:

a) measuring a biological effect of T3 mimetic having a carboxylic acid moiety wherein said biological effect is selected from the group consisting of the Ki relative to T3, effects on blood glucose level, effects on serum cholesterol level, effects on fat in the liver, liver specificity, and therapeutic index;

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- b) measuring the same biological effect measured in a) of a T3 mimetic having a phosphinic acid or prodrug moiety thereof; and
- c) comparing the results in steps a) and b); and
- d) selecting the T3 mimetic of step b) for further scientific evaluation.

## Homologous Displacement Reactions

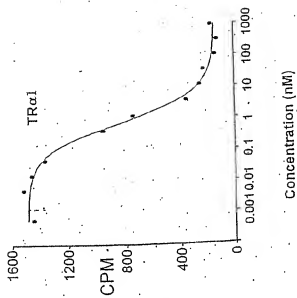


Fig. 1(a)

## T3 Binding Assay Results

## Homologous Displacement Reactions

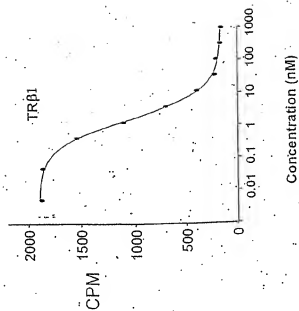


Fig. 1(b)

T3 Binding Assay Results



## Homologous Displacement Reactions

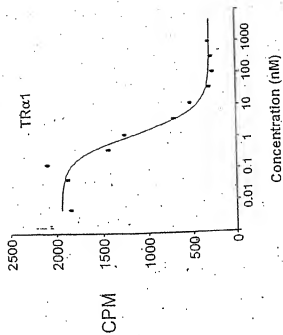


Fig. 1(c)

Compound 17 Binding Assay Results

## Homologous Displacement Reactions

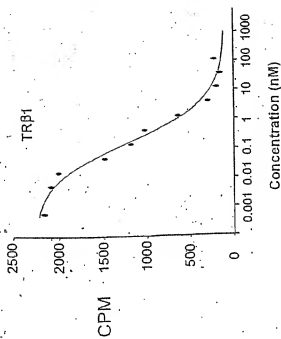


Fig. 1(d)

Compound 17 Binding Assay Results

## Homologous Displacement Reactions

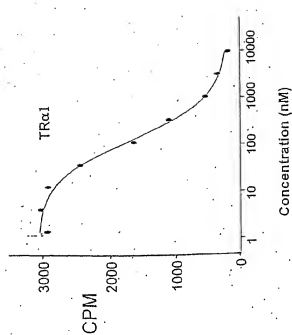


Fig. 1(e)

Compound 7 Binding Assay Results

## Homologous Displacement Reactions

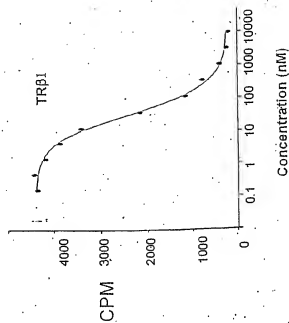


Fig. 1(f)

Compound 7 Binding Assay Results

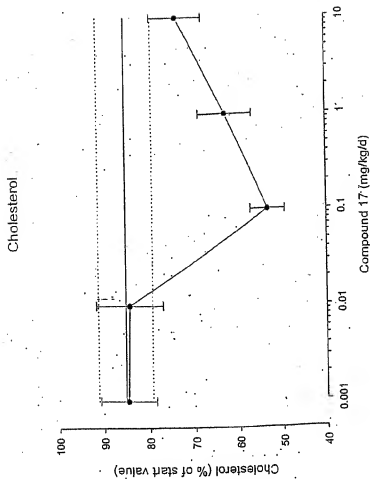


Fig. 2(a)  
Dose Response of Cholesterol to Compound 17  
in Cholesterol Fed Rats

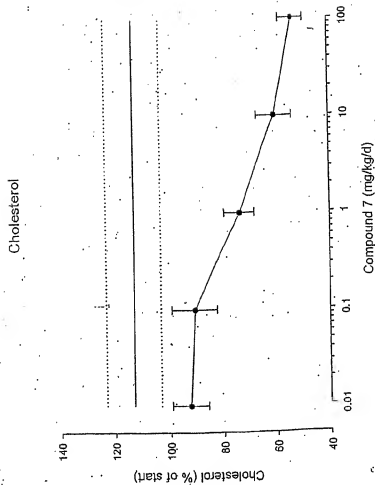


Fig. 2(b)  
Dose Response of Cholesterol to Compound 7  
in Cholesterol Fed Rats

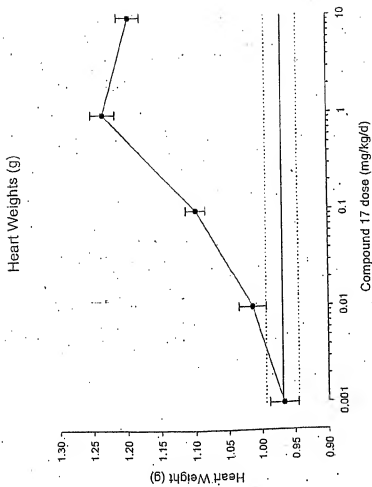


Fig. 3(a)  
Effect of Compound 17 on Heart Weight  
in Cholesterol Fed Rats

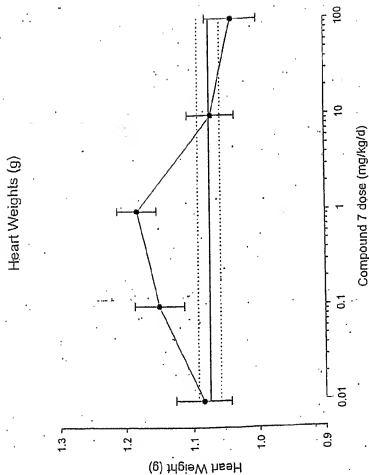


Fig. 3(b)  
Effect of Compound 7 on Heart Weight  
in Cholesterol Fed Rats



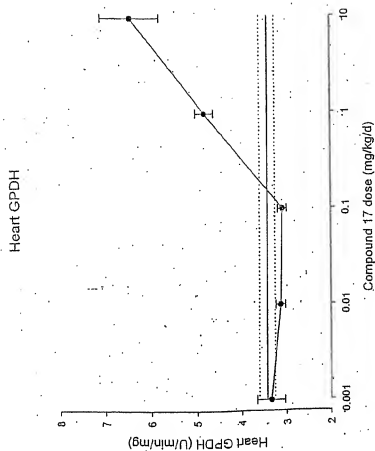


Fig. 4(a)  
Effect of Compound 17 on Cardiac GPDH Activity  
in Cholesterol Fed Rats

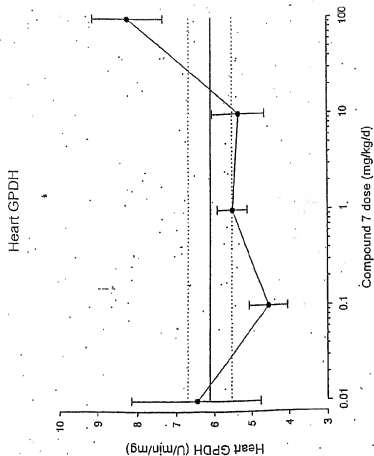


Fig. 4(b)  
Effect of Compound 7 on Cardiac GPDH Activity  
in Cholesterol Fed Rats

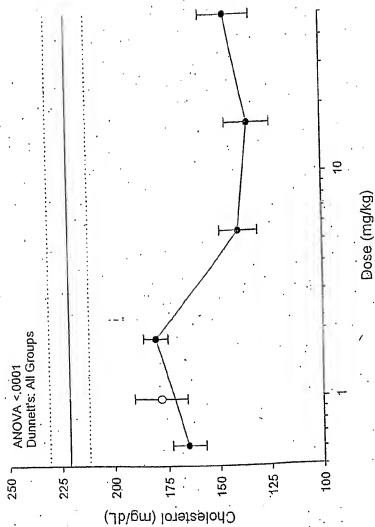


Fig. 5  
Effect of Compound 13-I-cis (○) and Compound 18 (●)  
on Cholesterol in Cholesterol Fed Rats